DSS

COPY

Date: June 14, 1994

From: Roger B. Cohen, M.D. RC 6/14/94

6/15/94

To: the File and Committee members

Subject: Product and clinical review of PLA 93-1057

I have reviewed the following volumes of the PLA in their entirety:

1-10: clinical summary and manufacturing

11-14 : pre-clinical studies

39-40: clinical summary of all trials including EPIC and clinical pharmacology

42-146: clinical data, individual trial summaries

42-62, 76-81, 144-148: phase 1

63-75, 82-93: phase 2

94-141: phase 3 (EPIC) trial

94: efficacy

95: safety

96: original protocol and amendments, analytic plans and amendments

98-111: narratives of patients experiencing efficacy or safety events

Supplementary volumes 1-3 (February 10, 1994): 6 month follow-up data

I have audited the following volumes of the PLA as described in the text of this review:

CD ROMS, volumes 1-6: photographs of case report forms (CRFs)

Volumes 112-140: selected line listings for EPIC trial, cross checked against data in CRFs in CD-ROMS

The following volumes contain references that I used as needed during the review:

15-16, 35-38,149-157

Introduction and background:

Rationale for clinical development: There is a consensus that platelets are the key participants in

thrombus formation that occurs on atherosclerotic plaques and on atherosclerotic plaques injured by PTCA. When thrombus forms on atherosclerotic lesions disrupted by PTCA, several acute complications may result. These include abrupt closure, recurrent ischemia, and MI. Thrombus formation may also play a role in re-stenosis, a more indolent complication of PTCA that occurs during the first few months following the procedure. Presently ASA and heparin, either alone or in combination, are used by most cardiologists who perform PTCA. Neither drug completely blocks platelet aggregation and acute and chronic complications of PTCA remain a significant problem. Additional anti-platelet therapies with different mechanisms of action would be useful in order to abolish participation of platelets in thrombus formation.

Clinical context: > 300,000 PTCA procedures in the USA in 1991. Abrupt closure of the newly opened artery occurs in as many as 10-20% of high risk PTCA procedures, leading to death, MI, or need for CABG or repeat PTCA ("urgent intervention").

There is a consensus in the cardiology community and literature that certain patients are at particularly high risk for complications from angioplasty. These patients include those with certain angiographic lesion patterns (types B and C, defined by the ACC/AHA task force), age >65, female sex, prior MI, diabetes, prior CABG, impaired LVF, and a history of hypertension. It is noteworthy that patients with many of these adverse characteristics are undergoing PTCA. Complications of PTCA may therefore increase.

Proposed indication in package insert (version dated 12/15/93):

[redacted]

Note that c7E3 is given with standard doses of heparin and ASA.

Similar and related products in clinical development:

Several related compounds (GPIIb/IIIa inhibitors) are under active clinical development, including:

[redacted]

Telios: IND 43788 for TP-9201

[redacted]

Hirudin and hirulog (Ciba-Geigy and Biogen), both direct anti-thrombins, may also be considered competing products as they are being developed as adjuncts for high risk angioplasty and related indications.

Part I: Product and pre-clinical review

Product: Fab fragment of chimeric mAb 7E3 — human)

It should be noted that the chimeric Fab and murine F(ab')2 and murine Fab were indistinguishable with respect to their ability to inhibit platelet aggregation in pre-clinical studies presented in the PLA.

Biological activity:

- GPIIb/IIIa is a member of the integrin receptor family

- GPIIb/IIIa is a platelet surface molecule that normally binds to fibrinogen and vWF and mediates platelet aggregation

- c7E3 binds to GPIIb/IIIa receptor on platelets (100,000 GPIIb/IIIa receptors per platelet)

- c7E3 binds to resting and activated platelets

- c7E3 Fab inhibits platelet aggregation without activating platelets

- c7E3 Fab does not interfere with GPIb mediated platelet adhesion

- c7E3 binding to platelets does not lead to measurable changes in platelet clearance (through the spleen, for example)

- Affinity of c7E3 for the GPIIb/IIIa receptor: K_d=5nM

Mechanism of action: The antibody does not bind to the ligand binding site itself (so-called RGD sequence). c7E3 binding prevents (by steric means) the interaction of fibrinogen or vWF with the receptor. The precise binding site is unknown.

Manufacture

Construction: Dr. Barry Coller's original mAb was murine. In order to produce a chimeric mAb, the sponsor [redacted]

Cell banks:

The cell banks have been characterized thoroughly according to the recommendations in the 1993 Cell Lines PTC (Appendix 1:2). The cell banks are positive for murine retroviruses, as expected. In particular, they express [redacted]) detected by the [redacted] assay and much lower levels of murine xenotropic retrovirus ([redacted] The purification scheme ([redacted] is adequately validated with satisfactory margins of clearance for the removal of these and a variety of other viruses.

Production: A vial of MWCB is expanded to [redacted] over [redacted] in order to inoculate the production fermenter ([redacted] . Continuous perfusion fermentation is performed in [redacted] and defined

medium (Appendix 1:3). The length of fermentation is limited to [redacted] because of a fall-off of mAb production after that time in some of the pilot cultures.

Purification

Purification can take up to [redacted] Many of the questions in our second information request (on product matters) relate to concerns that all of the many holding times and conditions for various process intermediates need to be validated adequately. The purification scheme includes a robust virus inactivation step ([redacted] and [redacted] that will remove viruses (Appendix 1:4).

A critical area that the sponsor needs to address in greater detail is bioburden testing and the reasons why bioburden was detected in some of the process intermediates in some of the lots (Appendix 1:5). Although the levels of bioburden in all cases were low and the process is not claimed to be an aseptic one, we feel that the control of bioburden needs to be more rigorous. [redacted] We have also recommended more comprehensive epidemiologic investigations of bioburden, including speciation and determination of source.

Process validation

The purification process was validated in a satisfactory manner for removal of various viruses, including enveloped murine retroviruses ([redacted] , as well as various potential low molecular weight protein contaminants and various reagents introduced during the manufacturing process (Appendix 1:6).

Removal of adventitious agents

A [redacted] virus validation using model viruses representing different physicochemical types ([redacted] demonstrated removal of [redacted] of virus by the purification process (Appendix 1:7-8).

Demonstration of biochemical equivalence for [redacted] and CBV lots

Product manufacture was switched during the pivotal trial from [redacted] to CBV. CBV is proposed as the licensed facility. For this reason establishment of bioequivalence was an issue during the PLA review. The issue was addressed in a satisfactory manner in the PLA by comprehensive biochemical, functional, pharmacokinetic, and clinical data demonstrating biochemical identity and equivalent biological activity. Product consistency at [redacted] and CBV, and between [redacted] and CBV, was demonstrated by means of the following analyses of FVP from 10 consecutive lots: [redacted] and final product control and release tests (Appendix 1:9). Side-by-side comparisons for each of these were presented in the PLA.

Stability studies

A stability program is in place that tests concentrated harvests, [redacted] and [redacted] The manufacturer has used an appropriate approach ([redacted] to define those tests that are "stability-indicating". The following tests were found to be "stability-indicating": [redacted] Data have been accumulated to date that support the following dating periods:

Concentrates: [redacted] in process, testing at [redacted] and [redacted] the sponsor intends to sek a dating period of [redacted]

[redacted], in progress; the sponsor intends to sek a dating period of [redacted]

Final vialed product: 2-8°C, [redacted] with current formulation, as of 12/15/93; the sponsor intends to seek a dating period of [redacted]

Reference standard: [redacted] as of 12/15/93. No proposed dating period was stated.

Additional real-time data are being collected using the tests in Appendix 1:10. Updated stability data will need to be submitted and reviewed prior to licensure in order to determine the proper dating periods.

Production of consistency lots at CBV

Two [redacted] lots have been fermented and purified entirely at CBV. One [redacted] lot was fermented at [redacted] and purified at CBV. The current plan is to ferment and purify a third [redacted] lot at CBV this summer (6/94) at the time of the CBER inspection. This would be the third consistency lot at the [redacted] scale. All 10 lots purified to date at [redacted] and CBV are biochemically and functionally similar using the broad range of tests in Appendix 1:9.

A summary of the lots produced at the 2 facilities and their disposition in the pivotal study is presented in Appendix 1:11.

Formulation

[redacted] The proposed formulation (Appendix 1:12) has been shown to be without adverse impact on the structure, activity, and stability of the product and was the exclusive formulation used in the EPIC trial. It is compatible with IV bags, tubing, and filters in common use, and with cardiac medications that are likely to be co-administered with c7E3.

Tests on final container (proposed)

Many of the tests listed in Appendix 1:13 will be incorporated into the eventual lot release protocols.

Summary of findings: The sponsor has demonstrated the ability to manufacture c7E3 consistently in its facility in the Netherlands. The product is biologically active, stable, and free of infectious and other contaminants. A sophisticated battery of biochemical and functional assays has been developed to characterize the product during manufacture and afterwards. The functional assays are somewhat unique for a biologic in that they very directly reflect the biological activity in the patient (e.g. [redacted]

———).

Questions from this reviewer on the pre-clinical portion that were used in drafting the second information request:

Volume 2:

1. Page 2: Storage of concentrated cell culture supernatants at —— is proposed. Have the stability data been submitted to validate the appropriateness of the proposed duration and temperature of storage. What is the current proposed upper time limit of storage based on the data obtained thus far?

2. Page 3: under what circumstances would pre-formulated bulk (PFB) be pooled?

3. ———

4. p.121: How long will it take for the cell population density to rise to ——— ? What are the proposed action limits is the cell population density rises too rapidly or too slowly?

5. p.121: Has microbial contamination at this stage ever occurred?

6. p.121: The additional 10-13 generations described in this section are 25% of the 40 generations that normally occur during a production run. Has this been validated? Is there not a drop-off in antibody production that occurs after day 35 (40 generations)? Please discuss.

7. 122: Have the media storage conditions been validated for maintenance of sterility?

8. p.125-26: How much time does it take for the production fermenter to reach —— cells/ml?

9. ———

10. p.127: Why is the dissolved oxygen concentration specification —— (Table 30)? The range should be narrowed based on actual manufacturing experience.

11. p.128: Have the holding time and conditions for ——— harvest been validated (——— for —— is proposed)?

12. p.133: What is the source of ——

13. p. 137: Has the holding period of process intermediates for —— at —— been validated for each manufacturing step?

14. [redacted]

15. [redacted]

16. Table 43, p.183 and p.185: We recommend that bioburden be tested (and found to be absent) prior to pooling of frozen PFB. Please comment.

17. p.206: Testing of FVP for product identity by [redacted] is proposed. [redacted]

volume 3:

18. Fig. 54 shows that the cell growth profile of lot S92D028 differs from the other lots at day [redacted] on. Similarly, mAb productivity, Figure 57, was [redacted] during some of this period. Please discuss and provide an explanation for these observations. The SOP for cell growth should be revised with action limits to terminate a culture that is not growing well.

19. [redacted]

20. p.255: [redacted] results should be analyzed by [redacted] Quantitative specifications, based on [redacted], should be used for lot release comparisons.

II: Background for Clinical review

Animal (model) studies: Dogs and monkeys were determined to be the most appropriate species for animal studies on the basis of affinity of antibody for the GPIIb/IIIa receptor. The monkey receptor is comparable to that found in humans while the dog receptor is 10-fold less avid. Various well-established models of thrombosis were studied. Various versions of 7E3 Fab were equally effective in preventing 1° thrombotic occlusion in a series of different animal models (using mechanical, electrolytic, or balloon angioplasty to cause arterial injury). The mAb was also active in preventing 2° thrombus formation in "thrombosis/rethrombosis" models. These studies suggested that 7E3 might have utility in the settings of acute MI, unstable angina, and PTCA. These studies also indicated that prevention of thrombosis requires blockade of > 80% of platelet GPIIb/IIIa receptors (and > 80% inhibition of platelet aggregation). This figure of 80% guided dose finding in the early phase 1 and 2 trials.

Cellular cross-reactivity studies: Cultured endothelial cells possess a receptor related to GPIIb/IIIa that can bind c7E3 (the vitronectin receptor). This receptor is not expressed on endothelial cells in normal blood vessels and no binding to blood vessels is detected *in vivo*. c7E3 does not block ability of cultured endothelial cells to organize into monolayers *in vitro* nor does it activate them (causing expression of E-selectin or ICAM-1 or *in vivo* release of vWF, tPA, or PAI-1). The majority of injected 7E3 binds to platelets, confirming that there is not a large competing endothelial cell pool. There has been a simmering controversy as to whether 7E3 binds to MAC-1 on monocytes and macrophages. Convincing data are presented in the PLA showing that binding to monocytes and macrophages is due to contaminating platelets or platelet fragments rather than specific receptors.

Overall clinical development program: Nineteen trials were conducted using all 3 versions of 7E3

(murine F(ab')2, murine Fab, and chimeric Fab. 2616 patients were enrolled of whom 1783 received antibody.

- 9 trials of c7E3 (6 phase 1, 2 phase 2, and 1 phase 3); 2358 patients enrolled; 1561 received mAb
- 414 patients received c7E3 from CBV, 922 patients from CSL;
- 67 patients received material fermented at CBV, processed at CSL.

Pharmacokinetic summary: 7E3 binds rapidly to platelets. The $t_{1/2_a}$ approximately 10 minutes (rapid binding to platelets). The $t_{1/2_b}$ approximately 30' (clearance of unbound antibody). Detectable antibody is found on platelets for up to 3 weeks. Platelet function returns to normal within hours of a bolus injection. In clinical trials bleeding time returned to <10' within 16-20 hours of cessation of infusion. Recovery of platelet aggregation to 80% of baseline required 50 hours.

Establishment of doses tested in the phase 3 trial: The proposed dose for licensure is c7E3 mAb as a 0.25 mg/kg IV bolus followed by 7E3 mAb @ 10 ug/min as a continuous IV infusion for 12 hours. The justification for proposed bolus dose is that the 0.25 mg/kg produces >80% receptor blockade. This level of receptor blockade was associated with efficacy in the pre-clinical models. Doses in excess of 0.25 mg/kg did not cause further receptor blockade or further inhibition of platelet aggregation. Targeting of levels of receptor blockade less than 80% was not considered in the clinical development program in view of the efficacy shown in the animal models at the higher (80%) level of blockade. The curves from the critical experiments are shown in Appendix 2:1.

A continuous infusion was determined in pre-clinical and clinical studies to be required in order to maintain functional receptor blockade. Two doses were explored: 5 and 10 ug/min. The 10 ug/min dose was effective at maintaining receptor blockade for the duration of an infusion (up to 96 hours) whereas the 5 ug/min dose was not. The result of the key experiment is shown in Appendix 2:2. The selection of a 12 hour infusion duration is based on clinical assessment of the period at risk for abrupt closure.

The ASA dose is the current standard of care, 325 mg po daily. The heparin dose is similarly based on the current standard of care: a 10,000-12,000 unit iv bolus, with additional 3000 unit boluses during the treatment period (12 hours) as required to maintain a therapeutic ACTor APTT, up to a total of 20,000 units (initial bolus + supplements).

Suportive evidence of efficacy (from phase 2): Centocor sponsored three phase 2 studies in 3 different patient populations (PTCA, unstable angina, and acute MI). Two of the studies used c7E3 Fab. The third study used murine 7E3 Fab. Only one of these studies was randomized and placebo-controlled (*vide infra*) and it is unlikely that that trial was blinded. From these 3 studies the sponsor defined retrospectively a composite endpoint of all cause mortality, MI, and need for urgent intervention. The composite endpoint occurred in 9/49 (18.4%) of control patients compared with 8/137 (5.8%) of 7E3-treated patients (p=0.017). The EPIC trial sought to demonstrate efficacy using the same composite endpoint. The design and outcome of the phase 2 trials are briefly summarized in the next section.

Summary of phase 2 trials:

1. Title: C0116T04: a phase 2 study of c7E3 mAb in the prevention of ischemic complications of high risk angioplasty

Study sites: 6, all US

Study design: phase 2, multi-center, open label, dose escalating, 2 stages

Patient population: coronary artery disease, unstable angina

Patients enrolled/evaluable: 56, all evaluable. Fifteen patients undergoing elective angioplasty were enrolled into stage I. Nine saline controls and 32 treated patients were enrolled into stage II. Stage II patients were intended to be at high risk for PTCA complications as follows: angina at rest with type B lesion with one adverse characteristic; diabetes, type B lesion with one adverse characteristic; type B lesion with ≥ 2 adverse characteristics; type C lesion; unstable angina or stable CAD with type B or C lesion.

Drug regimen: Stage I: 0.15, 0.2 and 0.25 mg/kg bolus in a total of 15 patients. Stage II: 0.25 mg/kg bolus followed by 10 ug/min for 6, 12, and 24 hours. Nine (9) patients received saline placebo. All patients received ASA and heparin per institutional guidelines.

1^0 objective: To evaluate the safety and preliminary efficacy of c7E3 in patients undergoing elective angioplasty who are at high risk for ischemic complications.

2^0 objectives: Assessment of platelet function with bolus and infusion regimens and recovery to normal of platelet function (*in vitro* and bleeding times).

Analytic plan: Clinical efficacy was to be assessed according to the occurrence of the following events: chest pain consistent with MI within 1 week of infusion; ischemic ECG changes; MI during hospitalization; need for urgent revascularization within 30 days; cardiac death within 30 days.

Results: 8/47 c7E3 treated patients had an ischemic event compared with 2/9 controls. No abrupt closures occurred in c7E3 treated patients compared with 1/9 in controls. Using the composite endpoint of the EPIC trial, 3/47 events occurred in c7E3 treated patients compared with 1/9 in controls (6.45 v 11.1%). Because of the small numbers and retrospective nature of the analyses, these data cannot be considered as evidence of efficacy.

2. Title: C0116T07, phase 2 randomized placebo controlled multicenter trial of c7E3 in patients scheduled for urgent PTCA due to unstable angina

Study sites: 7, all European

Study design: phase 2, multicenter, randomized, placebo-controlled; note that the performance of bleeding times probably made the blind impossible to maintain

Patient population: unstable angina, scheduled for urgent PTCA; the last ischemic episode was to have occurred within 12 hours preceding a qualifying angiogram showing a culprit lesion.

Patients enrolled/evaluable: 60; all evaluable

Drug regimen: Treatment was started within 2 hours after qualifying angiogram. Treatment was continued until 1 hour following the end of the PTCA with a minimum 18 hours treatment. The regimen was that proposed for licensure. Placebo patients received albumin. Patients received ASA, heparin and nitrates.

1° objectives:

a. Whether new episodes of ischemia are reduced or avoided with c7E3 during the 18-24 hour period between initiation of c7E3 and PTCA;

b. Angiographic differences after 18-24 hours between c7E3 and placebo patients;

c. Presence and extent of myocardial necrosis up to 72 hours after PTCA;

d. Outcome of PTCA.

Results: For the time period between the bolus injection and 48 hours post-PTCA, 19 placebo patients and 11 c7E3 treated patients experienced at least 1 major clinical event, including 4 MIs (all in placebo patients). Eighteen placebo patients and 11 c7E3 patients had new ischemia. Late clinical events were equivalent in both groups. There was no difference in the requirement for concomitant medications in the two groups. A blinded analysis by a Clinical Endpoints Committee of a composite efficacy endpoint (the same endpoint that was subsequently used in EPIC) showed a lower incidence of the composite endpoint in c7E3 treated patients (3%) versus placebo patients (23%, p=0.052).

Title: C0116T12, a phase 2, multicenter trial of murine mAb 7E3 Fab in patients with acute MI

Study sites: 6, all US

Study design: phase 2, multicenter, open label, dose escalation

Patient population: patients with acute MI undergoing coronary thrombolysis with 100 mg t-PA over 3 hours

Patients enrolled/evaluable: 72 patients total, 70 evaluable; 10 controls and 60 7E3 patients

Drug regimen: 0.1, 0.15, 0.2 or 0.25 mg/kg single bolus of 7E3 at various intervals (15, 6, and 3 hours) after t-PA; a saline bolus group was treated as well. The lowest dose (0.1 mg/kg) was given at the 15 hour interval only. The other 3 doses were studied at all 3 time intervals following t-PA. All patients received heparin and ASA.

1° objective: Safety and preliminary efficacy for prophylaxis of recurrent ischemia after thrombolytic therapy for acute MI. Thus, the endpoints were frequency of recurrent ischemic events and time to reperfusion. A composite recurrent ischemic event endpoint similar to but not identical to that used in EPIC was retrospectively defined as the cumulative occurrence of rest angina with diagnostic ECG changes, reinfarction, need for urgent intervention, or death. Also, assessment of infarct-related artery patency was performed in 37 mAb and 9 control patients.

Results: There was a trend for lower incidence of recurrent ischemic events in mAb patients. None of

the 14 patients who received mAb 3 hours following thrombolysis experienced an ischemic event compared to 2/10 controls. Greater patency of infarct related artery was seen in mAb patients. None of the results were statistically significant.

Part III: Clinical review of EPIC trial

Summary of phase 3 trial design and results:

Title: A phase 3 double-blind, placebo-controlled multicenter study of chimeric 7E3 Fab in patients undergoing high risk coronary angioplasty

General comment: this was a very well-designed and well-conducted trial. It demonstrates that the agent is potent with clear effects on the occurrence of clinical and safety endpoints. The randomization succeeded, the patient population is diverse, the statistical analysis was robust, and the analytic plan was followed. The clinical effects are important (prevention of MI and urgent revascularization procedures).

[redacted]

The 30-day and 6-month data from the EPIC trial were published in the New England Journal of Medicine (April 7, 1994) and the Lancet (April 9, 1994), respectively. It is worth noting that the protocol presented in both articles was faithful to the protocol submitted in the IND and its subsequent FDA-approved revisions, including endpoint definitions.

Study sites: 56 US sites

Enrollment dates: 11/26/91- 11/18/92

Study design: Phase 3, multi-center, three arm, multi-center, randomized, placebo-controlled, double blind study comparing a bolus to a bolus plus infusion regimen of c7E3.

Patient population: Patients ages 18-80 referred for elective or urgent PTCA for unstable angina and/or non-Q-wave MI; acute Q-wave MI; or high-risk morphologic/clinical characteristics. These 3 categories are considered to represent high risk situations.

The numbers in this section are expressed as a percent of all the patients enrolled in the study. Some of the patients were enrolled with more than 1 stratification criterion.

All MI/unstable angina, Σ= 42.5%, includes:

- Unstable angina at rest, 14.8%
- Unstable angina, recurrent, 6.8%
- MI, early post-infarct angina, 8.4%
- MI- direct intervention, 1.8%
- MI- direct rescue angioplasty, 1%
- MI- angioplasty of infarct related lesion within 7 days of MI, 25.4%

- MI evolving at baseline, 0.9%

Note that of the patients with "MI" in the preceding tabulation, only 25.3% (categories 1, 2, 4, 5, and 7 above) had acute MI or unstable angina. The remainder (categories 3 and 6) could more properly be characterized as having a history of recent MI.

High risk morphological/clinical, Σ=57.5%, includes:

- Stenosis with 2 or more type B (moderate success) lesions, 79.2%
- Stenosis with 1 or more type C (low success) lesion, 17%
- Age ≥65 + female sex + at least 1 type B lesion, 13.2%
- Diabetes and stenosis with at least 1 type B lesion, 19.9%

The trial entry criteria do seem to have succeeded in identifying a high-risk population. One reflection of this is that 31.5% of the patients enrolled experienced at least 1 component of the composite endpoint of death, MI or revascularization during the 6 month follow-up as follows: repeat PTCA, 18.3%; urgent PTCA, 4.9%; CABG, 10.1%; urgent CABG, 3.9%; MI, 8.4%; death, 3%.

Patients enrolled/evaluable: 2099 patients, all evaluable at 30 days except for 3 patients, one in each arm.

Patient follow-up:

At 30 days: >99%

At 6 months: 99% for survival, 98.4% for acute MI and revascularization procedures.

Unblinding: 82 patients total (4%): 22 placebo, 27 bolus, and 33 bolus plus infusion. The circumstances surrounding unblinding have been reviewed by examination of CRFs for each of these patients in the CD-ROM database that was submitted. Unblinding was nearly always for bleeding or in anticipation of major surgery (usually CABG). Those patients who were unblinded because of a planned or emergent CABG all proceeded to surgery indicating that unblinding in this context did not introduce bias.

Drug regimen: c7E3 and placebo were given intravenously by bolus and then by continuous intravenous (CIV) infusion. Patients were randomized to one of 3 regimens: 1) placebo bolus and 12 hours of CIV placebo; 2) c7E3 Fab bolus (0.25 mg/kg) and 12 hour CIV placebo; 3) c7E3 Fab bolus (0.25 mg/kg) and 12 hour CIV c7E3 Fab (10 ug/min). Treatment was started with administration of the bolus dose immediately prior to PTCA, at least 10' but no later than 60' before the start of PTCA (defined as balloon inflation or atherectomy cut).

Concomitant medications: ASA 325 mg daily; heparin 10,000-12,000 unit bolus in the cardiac catheterization lab with additional 5000 unit boluses as needed, guided by ACT and APTT values, to a maximum of 20,000 units.

1^0 objective: To determine the efficacy of 2 regimens of c7E3 Fab in reducing the complications of PTCA, i.e. MI, need for urgent intervention, or death, within 30 days following PTCA. **The 1^0 efficacy criterion was the prevention of any one component of a composite primary endpoint**

defined as the occurrence of any one of the following events within 30 days of PTCA: MI, recurrent ischemic event requiring an urgent intervention (PTCA, CABG, IABP, stent) or all cause-mortality.

2° objectives (prospectively ranked by order of importance): analyses of components of 1° endpoint (all-cause mortality, cardiac mortality plus non-fatal MI, MI, urgent intervention, cause-specific mortality); analysis of 1° endpoint by MI or unstable angina versus other high risk group; analyses of 1° endpoint by presence or absence of thrombus; replication of 1° endpoint analysis in 2 independent sets of data; ischemic episodes; analyses of 1° endpoint by age, sex, study site; 6 month follow-up; economic analysis

1° efficacy endpoint for long-term follow-up (6 month): Two versions of the primary endpoint were examined: the original composite primary endpoint and a slightly modified endpoint examining all-cause mortality, MI, and the occurrence of any revascularization procedure (urgent and non-urgent). The sponsor also chose to exclude stents and IABPs from the 6-month analysis, which is reasonable as there were very few (1 of each) and they were always related to PTCA or CABG.

Analytic plan: An intention-to-treat analysis was used throughout. Tests for treatment differences were performed in 2 stages: 1) Generalized logrank test for trend across treatment arms; 2) If a positive trend was detected, pairwise logrank tests were performed comparing placebo with each experimental arm.. Survival analysis (K-M method) was performed for 1° and 2° analyses.

It is worth noting that the analytic plan underwent several revisions, all of which were reviewed by CBER. The final version of the plan was approved by CBER prior to unblinding of the database. The various versions of the analytic plan are presented in volume 96. Much of the focus of these revisions was on the criteria for diagnosis of acute MI, one of the endpoint components for the primary efficacy analysis. One result of the revisions was to make the criteria for MI more specific for MI while sacrificing some sensitivity. This was accomplished by eliminating chest pain as a criterion and making the thresholds for CPK enzyme elevations higher. Despite the reduction in event rates brought about by these changes, the EPIC trial showed convincing efficacy based on the analysis of the primary composite endpoint.

Methods to ensure data integrity:

1. A Clinical Endpoints Committee (CEC) was established by the sponsor to review all CRFs for the occurrence of a primary endpoint and major safety events. All patients were screened by computer and by the CEC coordinator. The coordinator and CEC members remained blinded to treatment arm and interim results for the entire study. The CEC then reviewed abstracted clinical data. Each patient with a suspected endpoint was reviewed by two physician committee members. If they could not agree on a classification, the full committee reviewed the data. For patients with an efficacy and safety endpoint, two different physicians reviewed each component independently. The efficacy component was always reviewed first.

A second Safety and Efficacy Monitoring Committee (SEMC), distinct from the CEC and Centocor, was established to review and make recommendations regarding study termination or modification based on the outcome of the interim analyses.

2. Interim analyses: The 1st interim analysis was on July 29, 1992. 698 CRFs were

included. The second interim analysis was on August 26, 1992. 1336 patients were reviewed (754 patients with CRF data, the rest from summary safety data forms and unmonitored CRFs). Both times the SEMC recommended that the study proceed without modification.

On both occasions analysis of the primary efficacy endpoint was performed. At the first interim analysis the treatment code was broken but no statistical tests were performed. At the second interim analysis efficacy was examined to evaluate the probability of a positive efficacy finding at the end of the trial. The latter analysis had also been specified in the analytic plan.

3. CBER audits of study sites and CEC/SEMC proceedings. The audits were guided by questions from the PLA clinical reviewers (see Appendix 2:3). Audits of 7 study sites accounting for more than 1/3 of enrolled patients are complete. Centocor itself was audited as well in order to examine the correspondence and minutes of the CEC and SEMC proceedings.

3. Provision of CD-ROM disks containing photographs of original CRFs on every patient in the EPIC study, with CRFs for patients experiencing efficacy or safety endpoints grouped together for ease of review.

Efficacy data:

Note that the statistical tests performed on each of the Tables presented in this section have been verified by the CBER PLA statistician.

Thirty day follow-up

Primary analysis of the composite endpoint, intention to treat of all randomized patients

The bolus plus infusion regimen led to a statistically significant decrease in the occurrence of the composite endpoint compared to both the placebo and bolus arms (Appendi)x 2:4.

It should be noted that the majority (81%) of efficacy endpoints occurred within 2 days (82% placebo, 79.7% bolus, 81.4% bolus + infusion)

Secondary analyses (all prospectively defined, including rank order of importance)

For pre-specified components of the composite endpoint

The number of deaths in the trial was small and neither regimen had any effect on mortality. The greatest effects were observed in the MI/unstable angina and urgent intervention components (Appendix 2:4).

According to type of MI

Within the MI component of the composite endpoint, reduction in Q wave MI was the most compelling and statistically significant. This is an important observation because Q-wave MIs are associated with the greatest amount of myocardial necrosis and risk of subsequent heart failure, arrhythmia, and death (Appendix 2:5).

According to type of urgent intervention

Within the urgent intervention component, reduction in urgent PTCA was most prominent (Appendix 2:6). There was also a favorable trend in favor of the bolus plus infusion arm for a reduction in need for urgent CABG. Few patients in the study had an endpoint IABP or stent.

Timing of urgent interventions

The K-M curves (Appendix 2:7) indicate that urgent PTCAs did not occur until 4 hours after bolus and 11 hours after bolus plus infusion treatment. This timing suggests that the bolus regimen had some beneficial effect but only for a few hours. Interestingly, earlier studies had shown that platelet aggregation recovered to ~50% of baseline 4 hours following a bolus injection. Therefore, the lag in endpoint occurrence in the bolus regimen is additional evidence of product activity and also provides a strong justification for the bolus plus infusion regimen.

Characteristics of ischemia in patients requiring urgent PTCA

One potential criticism of the trial is that urgent PTCA is a potentially "soft" (subjective) endpoint component. A number of analyses were performed to characterize the urgency of PTCAs contributing to this endpoint component. The events leading to urgent PTCA in the trial were of a serious nature (Appendix 2:8). Symptoms provoking urgent PTCA included: chest pain >50' (75%); ECG changes (58.3%); NTG Rx (81.3%); MSO_4 Rx (29.2%); MI (24/62 procedures (38.7%)). All but 2 patients with an urgent PTCA endpoint had ischemic episodes reported. The 2 exceptions had documented abrupt closure before leaving the cath lab. The CRFs on CD-ROM confirm the urgent nature of the PTCAs performed in the trial. The urgent PTCAs are clearly distinguished from routine, non-urgent PTCA (most of which were staged procedures to treat multiple lesions in multiple arteries).

Furthermore, urgent PTCA was not a benign procedure. Many were associated with serious and life-threatening complications. (Appendix 2:9).

Primary endpoint event rates by risk status

Primary endpoint event rates were reduced by c7E3 without regard to risk status. However, the reduction was much more prominent in the MI/unstable angina patients (Appendix 2:10). One criticism of the study is that a minority of patients (25.3%) had unstable angina and MI. It would have been helpful to have enrolled a larger number of these patients into the trial. This is particularly true as one *post hoc* analysis of the unstable angina subgroup suggested a benefit for c7E3 on mortality as well as on the occurrence of MI.

Six month follow-up (analyzed as first 30 days, days 3-180, and days 31-180)

The initial efficacy benefit is maintained for the entire 6 months of follow-up. The survival

curves for the endpoint events remain divergent. This may reflect the ability of c7E3 to reduce clinical re-stenosis although this trial did not specifically examine the patients angiographically, which would have been required to make such a claim. Efficacy over the entire 6 months was mostly related to a reduction in the need for revascularization rather than death or MI. Deaths were the same across all 3 arms throughout the 6 month period and the MI benefit occurred within the 1st 2 days. Positive trends were noted in the incidence of repeat PTCA, urgent PTCA, and patients requiring repeat PTCA for the artery treated in the original PTCA after day 2 and after day 30, and over the entire 6 month period.

Primary composite endpoint event rates

This analysis shows that most of the benefit for acute events occurs early. The trends for the later time periods (after day 2) are positive but statistically non-significant (Appendix 2:11-12).

Primary composite endpoint (revised for 6 month analysis) event rates

The composite endpoint for this analysis was revised slightly (prospectively, as noted in the final analytic plan) to include death, MI, or any revascularization procedure (urgent and non-urgent). Though the difference is not statistically significant (p=0.07), there is a clear trend towards a decreased need for any revascularization procedure (15.3 versus 19.3%) in the bolus plus infusion arm compared to placebo for the 31-180 day follow-up period (Appendix 2:13-14). This analysis suggests that some of the benefit of c7E3 is delayed and may reflect effects on re-stenosis.

Patients with procedures on initial procedure related artery (PRA)

There are consistent reductions over the entire 6 month period in the need for revascularization procedures on the artery that was treated by PTCA in the presence of c7E3 (Appendix 2:15-16). This analysis also provides suggestive evidence for benefit on clinical re-stenosis.

According to risk status at study entry

The benefit over the entire 6 months is seen in both of the 1° risk strata. However, Appendix 2:18, for example, shows that the benefit to patients with unstable angina/MI accrues during the first 30 days only. In contrast, some of the benefit to patients in the other risk strata accrues between the 30 day and 180 day follow-up (Appendix 2:17). This contrasting pattern of benefit may also reflect an impact on re-stenosis if re-stenosis is more likely in anatomically challenging lesions.

According to number of segments treated

It is noteworthy that patients requiring an index PTCA of >1 segment did not benefit from c7E3 during any of the follow-up periods (Appendix 2:19-20). This is an important observation because elimination of these patients from the target population may improve the therapeutic index for the remaining patients.

According to duration of index PTCA

It is also of note that patients with PTCA duration > 70' also did not benefit during any of the follow-up periods (Appendix 2:21). The long PTCA duration likely reflects technical problems with PTCA, possibly related to lesion characteristics, the need to dilate > 1 segment, etc. This is an important observation because elimination of these patients from the target population may improve the therapeutic index for the remaining patients.

Additional analyses included in the 30 day results:

There was no site-treatment interaction.

Patients with diabetes, renal disease, and peripheral vascular disease were examined separately and showed no benefit from either c7E3 regimen. Elimination of these patients from the target population also might improve the therapeutic index of c7E3.

(Appendix 2:22). Lighter patients experienced more endpoints than heavier patients in the bolus plus infusion arm. Another way of putting this is that heavier patients seemed to derive more benefit from c7E3. The sponsor offered the *post hoc* explanation that men weighing <75 kg with diabetes or renal disease made up the majority of the lighter patients. other subgroup analyses suggested that patients with diabetes and renal disease did not benefit from c7E3. The problem with this analysis is that the numbers of patients in each category was very small and the analyses were all *post hoc*.

Patients with at least 1 type C lesion did not appear to benefit. Patients with initially successful PTCA were most likely to benefit whereas patients with unsuccessful PTCA experienced no benefit. It may be possible to use these data to eliminate groups of patients, in addition to those discussed above, from any or from continued therapy with c7E3 and thereby improve the therapeutic index.

There was no relationship between initial or total heparin dose and occurrence of a primary endpoint in any of the treatment groups (Appendix 2:23-24). Therefore, heparin dose does not appear to play a major role in the efficacy of c7E3, in contrast to the incidence of bleeding (*vide infra*) in which it appears to play a more critical role. This observation is quite important in that it provides justification for efforts to adjust the heparin dose in order to decrease the incidence of bleeding and suggests that such efforts will not have an adverse impact on c7E3 efficacy.

Other observations:

The bolus plus infusion regimen also reduced the number of patients experiencing multiple 1° endpoint events; 89 placebo patients experienced 135 1° endpoint events compared with 59 bolus plus infusion patients who experienced 77 1° endpoint events. Of the 89 placebo patients, 35 (39.3%) had >1 event compared to 15 (25.4%) of 59 bolus plus infusion patients.

None of the patients in bolus plus infusion group who required an urgent PTCA had

thrombus compared with 62.5% of placebo and 47.1% of bolus patients. Also, none of the patients in bolus plus infusion group who required an urgent PTCA required thrombolytic therapy.

These observations reiterate the internal consistency and biologic plausibility of the trial results.

Safety data

30 day safety data:

Deaths and strokes

The numbers of deaths (33) and strokes (hemorrhagic and non-hemorrhagic, Σ=14) were similar among treatment groups (Appendix 3:1).

Bleeding

Criteria developed in the TIMI trials (Appendix 3:2) and now in widespread use for trials of thrombolytics were used to rate the severity of bleeding. The use of these criteria allows one to gauge the severity of bleeding in EPIC in comparison to other trials of PTCA and/or thrombolytics in similar patient populations (see Appendix 3:12-14).

There were 222 major bleeds (CABG and non-CABG related) and 295 minor bleeds. The frequency of major bleeds was doubled in bolus plus infusion group (14%) compared with placebo (6.6%). Minor bleeds were also more frequent in bolus plus infusion group (16.9%) v placebo (9.8%). The incidence of bleeding in the bolus group was intermediate between that seen in the bolus plus infusion and placebo groups (Appendix 3:3).

Sixty-six (66) of the major bleeds were associated with CABG. Major bleeds associated with CABG were not increased in bolus plus infusion group relative to placebo. When CABG associated bleeds are separated out, the incidence of major bleeds was increased 3-fold in bolus plus infusion group (10.6%) v placebo (3.3%) (Appendix 3:4). This higher figure of 3-fold probably represents the more realistic impact of c7E3 on bleeding risk.

The majority of bleeds in the bolus and bolus plus infusion groups occurred within the 1st 36 hours whereas placebo associated major bleeds were equally distributed before and after 36 hour landmark. This observation also clearly links occurrence of bleeding to the administration of c7E3.

Clinical consequences of bleeding

Ten (10) patients with major bleeds died: 5 bolus plus infusion, 3 bolus, and 2 placebo patients. Of the ten deaths, two were judged by the SEMC to have been the result of bleeding (1 bolus plus infusion and 1 placebo patient, both from hemorrhagic strokes).

Surgery for bleeding was not more frequent in the c7E3 arms. Three (3) craniotomies were performed (1 in each arm of study) and a single patient (placebo) required repair of an

AAA. The other surgeries for bleeding were all repairs of vascular access sites. The absolute number of surgical repairs was greater in the bolus plus infusion arm but the relative incidence (relative to bleeding) was the same in all 3 arms (Appendix 3:5).

Diagnostic procedures (non-invasive cardiac, vascular, and abdominal) procedures were more numerous in bolus plus infusion group versus placebo (27.1 v 19.3%). In particular, more endoscopy was performed (to evaluate hematemesis) in bolus plus infusion group versus placebo (1.8 v 0.9%).

The severity of bleeding did not differ in a statistically significant manner among the treatment groups. Transfusion of >5 units PRBCs was required in 8 bolus plus infusion patients, 6 bolus patients, and 2 placebo patients.

Other miscellaneous consequences of bleeding were hypotension, pulmonary edema, and prolonged hospital stay (7 days median in patients with major bleeds versus 3 days in patients without major bleed).

Sites of bleeding (Appendix 3:5)

More than >70% of bleeding was from arterial access sites

The GI and GU tracts were the most common sites for spontaneous bleeding.

The sites of minor bleeding were similar to those for major bleeds.

Interestingly, the increase in spontaneous major organ (GI, GU) bleeding occurred almost entirely in patients <75 kg in the bolus plus infusion arm. This provides another hint that there is an important interaction of bleeding with weight and factors such as heparin dose that are linked to weight.

Factors that may influence risk of bleeding

A variety of factors were examined. Those that stood out are presented here.

Heparin

An initial bolus dose of >10000 units was associated with more bleeding. A total heparin dose of ≥10000 units was also associated with more bleeding. These observations are reflected in the parallel observations that bleeding risk was associated with higher ACT and APTT levels (Appendix 3:6-7).

Demographic factors

There was more bleeding in women than men in the bolus plus infusion arm (10.3 v 6.5%). Bleeding was more common in the elderly (≥ 65) in the bolus plus infusion group. Major bleeds were most frequent in females ≥ 65 (20.7%) in the bolus plus infusion arm (Appendix 3:8). Elderly women have been found to be at risk of

bleeding from anticoagulant therapy generally in many clinical settings so that this latter observation is not surprising.

Other risk factors suggested by the analysis:

Patients with prior GI disease, peripheral vascular disease, prolonged PTCA, receiving rescue PTCA, receiving thrombolytics post-PTCA, and receiving thrombolytics during PTCA had a higher risk of major bleeding if they also received c7E3.

Weight

There was a strong statistically significant association of bleeding and body weight in the bolus plus infusion arm (Appendix 3:9). Similar non-statistically significant trends were seen in the bolus and placebo arms. For patients in the high weight group, differences in major bleeding events among treatment groups were much smaller than for low-weight patients. The incidence of major bleeds was most notable in males <75 kg (16.1 v 3.1%, bolus plus infusion versus placebo, p=0.001). A similar trend (19.6 v 13.8%) was seen in women though not as marked and not statistically significant, perhaps because women are simply at higher risk for bleeding if they receive heparin.

There was also a negative relationship between ACT and body weight; the lowest weight group had the highest median ACT (Appendix 3:10).

Taken together, these observations suggest that adjustment of the heparin dose on a weight basis may be one appropriate means to decrease the incidence of bleeding. As noted earlier (Appendix 2:23-24), there do not appear to be any important relationships between heparin dose and efficacy.

Other safety observations:

Thrombocytopenia

There was a statistically non-significant trend for a higher incidence of severe thrombocytopenia in the bolus plus infusion arm. The majority of severe thrombocytopenia occurred within the first 24 hours. Few episodes of thrombocytopenia occurred between 7-30 days in any group. Two major bleeding episodes occurred in thrombocytopenic patients in the bolus plus infusion arm. More platelet transfusions were required in the bolus plus infusion group.

Hypotension

Blood pressure decreases were more common in bolus plus infusion group (21 v 12%, bolus plus infusion versus placebo). It is likely that many of these episodes were related to bleeding.

Host response (immunogenicity)

A 5-6% incidence of low titer HACA [<1:1600] was measured in the phase 3 trial; 6 bolus plus infusion patients had HACA titers between 1:6400 and 1:51200. This low incidence of anti-globulins suggests that the strategy of producing a chimeric antibody to lower immunogenicity succeeded and that re-treatment with c7E3 may be possible.

Other allergic responses were very rare in all 3 groups.

Assessment of benefit:risk ratio:

First, the sponsor presented two types of analyses. First, in Appendix 3:11 the sponsor compares the incidence of major bleeding in other published trials involving PTCA and/or thrombolytic therapy. The incidence of bleeding is also compared to that seen in a group of trials involving stent placement (in patients with threatened or actual complications of PTCA). In the 3 trials that used the TIMI criteria the incidence of major bleeding in the EPIC trial is quite comparable to the other 2 trials as was the incidence of hemorrhagic stroke. Changes in hemoglobin/hematocrit, when reported, are also comparable to the those seen in EPIC as was the total number of patients requiring transfusions.

Second, the sponsor prepared a risk/benefit hierarchy for the 30-day and 6-month follow-up periods in which the predicted net benefit per 1000 treated patients was estimated using all of the important efficacy and safety endpoints (Appendix 3:11-13). Taking into account all the efficacy endpoints and major bleeding endpoints, the predicted net benefit per 1000 treated patients is 33 patients. At the 6-month landmark the predicted net benefit is 74 patients. Of course, this analysis does not take into account minor bleeding episodes, the need for more diagnostic procedures, and the prolongation of hospital stay caused by c7E3, which would diminsh the apparent benefits. It also does not take into account the effects of eliminating patients who showed no benefit from c7E3, which would enhance the apparent benefit.

Reviewer's summary of safety and efficacy:

The EPIC trial enrolled 2099 patients into 3 arms of a randomized, placebo-controlled doule blind study to test the efficacy of two doses of c7E3 versus placebo in patients undergoing "high-risk angioplasty" at 56 centers in the US. The trial was well conducted with nearly perfect follow-up at 30 days (99%) and 6 months (>98%). Numerous mechanisms were in place to ensure data integrity and unbiased assessment of safety and efficacy endpoints. The analytic plan was designed with CBER statistical and clinical guidance. The final analytic plan was submitted to and approved by CBER on January 29, 1993 prior to unblinding of the database. Two interim analyses for safety were performed in July and August of 1992.

Based on an intent-to-treat analysis c7E3 was found to reduce the occurrence of a composite endpoint defined as death, MI, or urgent intervention in a statistically significant fashion when given as a bolus plus infusion but not as a bolus dose. The drug did not reduce mortality, which was very low in all 3 arms of the study and the study was not powered to show benefit on mortality. Benefit was most marked in the MI and urgent intervention components of the composite endpoint and the benefits were statistically significant in each of these sub-groups. These benefits were seen across all groups enrolled in the trial without evidence of differential efficacy according to age, sex, study sites, risk groups, and patients with or without visible coronary thrombus.

A large number of pre-specified and *post hoc* secondary analyses were performed as well. The majority of these analyses showed benefit for c7E3. The internal consistency of the trial results enhances the plausibility of the 1° analysis for efficacy.

The long-term follow-up showed that the initial efficacy benefit was maintained for at least 6 months. Furthermore, there is some evidence of efficacy (prevention of the need for revascularization) beyond the first 48 hours following treatment and between the 30 day and 180 day landmarks. These extremely interesting observations suggest that c7E3 may reduce the rate of delayed complications of PTCA such as coronary artery re-stenosis in addition to it effects on more acute events.

Benefit came at the expense of a significant amount of clinically important bleeding. The incidence of intracranial bleeding and the incidence of bleeding associated with death were not increased in the treatment arms. The incidence of both of these grave complications was very low in the study. The 95% confidence intervals for intracmail hemorrhage (2 out of 678 treated olus plus infusion patients) are 0.03-1.1%. However, major bleeding was increased 2-3 fold in the bolus plus infusion arm compared to placebo. More than 70% of the episodes of major bleeding were at the arterial access site in the groin. The remainder were spontaneous hematemesis or hematuria and a few retroperitoneal bleeds. Bleeding was not more severe in c7E3 treated patients who required CABG. Bleeding in c7E3 treated patients did not lead to an increased frequency of surgery though it did lead to a greater number of diagnostic procedures. Bleeding also prolonged hospital stay.

Despite the bleeding, the benefit to risk ratio appears to be in favor of c7E3 for the following reasons: 1) the complications that c7E3 prevents such as Q-wave MI, are irreversible and may lead to death and 2) bleeding is predominantly at the arterial access site and therefore amenable to local control measures and replacement therapy with blood products.

A number of analyses by the sponsor and CBER also suggest that there may be ways to reduce the risk of bleeding. First, we and the sponsor have identified through pre-specified and *post hoc* analyses groups of patients who experienced diminshed or no benefit from the agent (e.g. patients with failed angioplasties, patients requiring dilatation of more than 1 lesion in an artery, diabetics, and patients with renal failure), leaving them with mostly exposure to the risks of the agent. Perhaps these groups should be eliminated from the target population. In the case of patients with failed angioplasties or unattempted angioplasties, the drug could be stopped prior to the 12 hour infusion. Second, a variety of observations and analyses by us and the sponsor suggest that adjustment of the dose of heparin may decrease the risk of bleeding without compromising efficacy.

In summary, the sponsor has demonstrated safety and efficacy of c7E3 in well-conducted clinical trial.

[redacted]

Clinical comments and questions used to draft the information request dated 4/29/94:

1. [redacted]

2. Please provide the data that support 36 hours as the period of greatest risk for re-occlusion.

3.

4. Please assess the trends for efficacy and major bleeding episodes in the 3 largest centers; in

5. Is there any relationship between the occurrence of thrombocytopenia to total heparin dose, intensity of anti-coagulation (APTT, ACT), duration of heparin infusion, etc.?

6. Please explain further the statement on page 56, vol 95: "Because with long heparin infusions, the bleeding rates are similar among the three treatment groups, the bleeding that occurred in the bolus plus infusion group may be related more to the duration of the heparin treatment than to the c7E3 Fab treatment."

7. Does 7E3 bind differently to activated platelets?

8. Are pharmacokinetics different in patients with a) activated platelets?, b) renal failure, c) diabetes mellitus, d) known peripheral vascular disease, e) very high or very low platelet counts (within the normal range), f) other inflammatory states?

9. Recalculate the safety data (major and minor bleeds, transfusion requirements) excluding patients with unsuccessful PTCA. [Patients with unsuccessful PTCA who had infusions discontinued could be considered as receiving bolus treatment only]. Please perform a similar analysis excluding patients with unsuccessful PTCA or >1 segment treated.

10. Of the patients experiencing the urgent PTCA endpoint, what percentage went on to have acute MI? What percentage had documented closure of the procedure related artery?

11. Please analyze the primary efficacy and safety endpoints according to the number of balloon inflations (use the dichotomous categories of >4 and

12. Please analyze the primary efficacy and safety data according to the total inflation time (use the dichotomous categories of <180s and

13.

14. Please analyze the primary efficacy and safety endpoints by APTT (use the dichotomous categories of ≤90s and >90s).

15. Was high blood pressure examined as an independent risk factor for major bleeds?

16. The effect of c7E3 on platelet survival was studied in C0116T11, a study done with but not with heparin. Please comment on the [redacted] of this study in the context of c7E3 administration with heparin and [redacted] in the EPIC study and in the proposed labeling.

17. Please perform regression analyses on the influence of ACT/APTT/heparin dose/duration of heparin infusion on c7E3 efficacy.

18. [redacted]

19. [redacted]

20. [redacted]

21. [redacted]

22. [redacted]

23. [redacted]

24. [redacted]

25. [redacted]

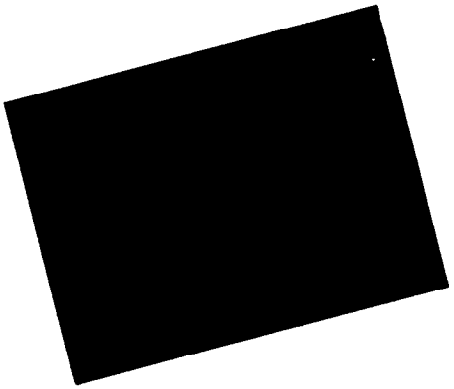
26. [redacted]

27. [redacted]

THIS PAGE WAS DETERMINED TO BE NOT RELEASABLE

14 pages

Appendix 2: Efficacy



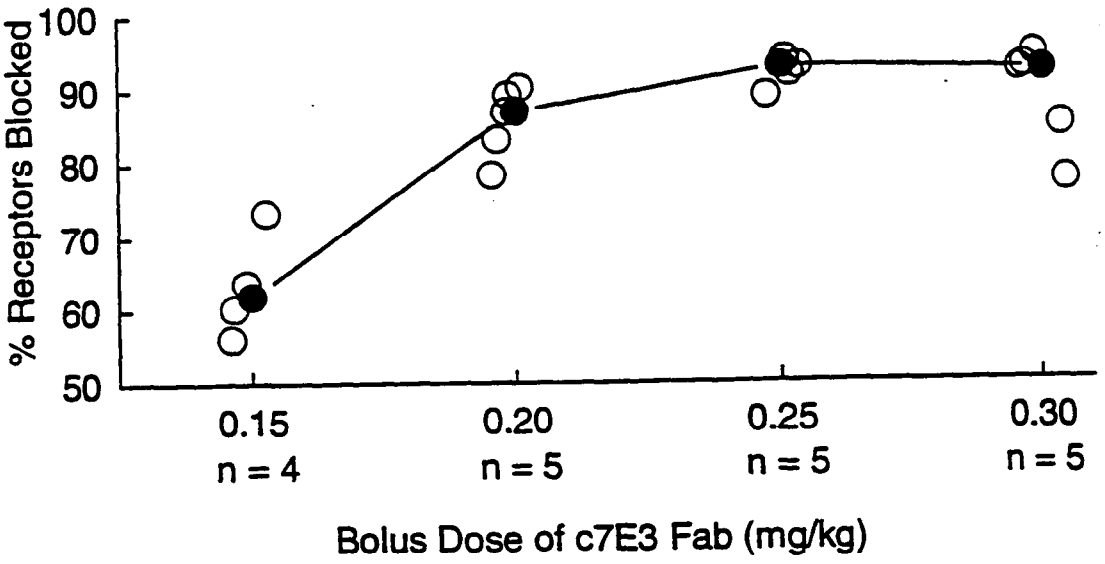


Figure 3

Effects of c7E3 Fab administered as a single bolus dose regimen on platelet GPIIb/IIIa receptor blockade at 2 hours post-injection. Results in filled circles depict the median percentage of platelet GPIIb/IIIa receptors blocked by c7E3 Fab. Results for individual patients are depicted by the open circles.

For the majority of patients who received a bolus plus 10 μg/min continuous infusion, GPIIb/IIIa receptor blockade was maintained in excess of 80% throughout the duration of the infusion, but was not maintained in the group receiving the 5 μg/min infusion rate. Among the 5 regimens receiving the 10 μg/min infusion rate, there was essentially no difference in the level of response during the infusion period. The data for the 5 μg/min and 10 μg/min infusion rates are shown for the 24 hour infusion groups in Figure 4. The degree of GPIIb/IIIa receptor blockade fell relatively slowly at a constant rate after the infusions were stopped.

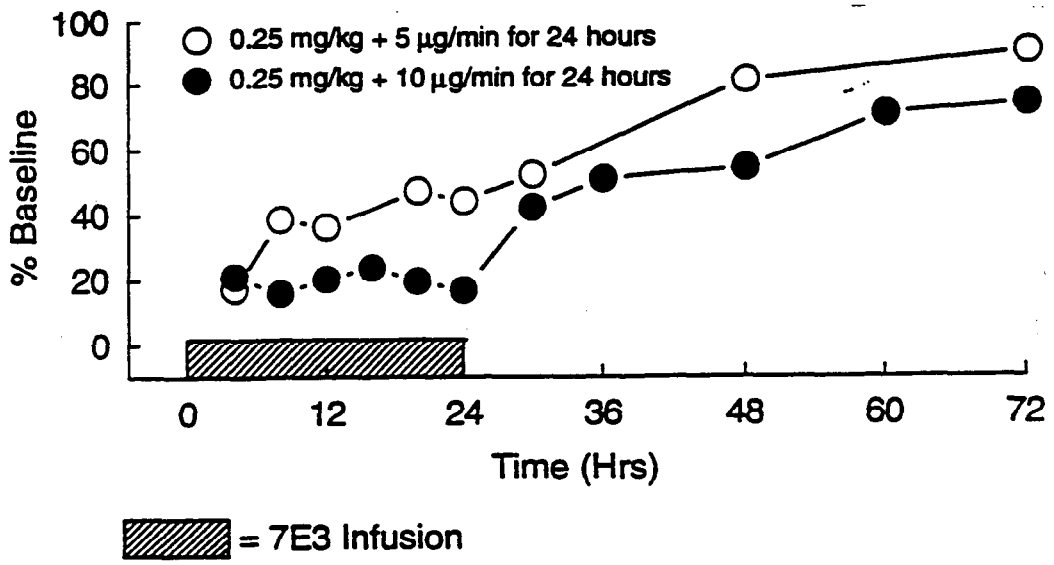


Figure 6

Median results for *ex vivo* platelet aggregation in response to 20 µM ADP in patients receiving a bolus dose of 0.25 mg/kg followed by a continuous infusion of 5 µg/minute or 10 µg/minute for 24 hours. There were 5 patients in each group.

Bleeding Time: In the single bolus dosage groups, median bleeding time at 2-hours post-injection were 9, 19, >30, and >30 minutes for the 0.15, 0.20, 0.25, and 0.30 mg/kg doses, respectively. Results of regression analysis at the 2-hour sampling time showed a significant relationship between bleeding time and c7E3 Fab dose ($p<0.001$; $r=0.82$). Bleeding time following injection of c7E3 Fab demonstrated a pattern similar to that observed for both GPIIb/IIIa receptor binding and *ex vivo* ADP-induced platelet aggregation. The effects of c7E3 Fab on bleeding time declined rapidly after the bolus dose in most patients. Median bleeding time decreased to approximately 10 minutes by 12 hours post-injection.

Bleeding time in patients receiving the bolus dose followed with continuous infusion was prolonged to greater than 30 minutes throughout most of the infusion period in all but one patient receiving the 10 µg/min infusion rate. At the 5 µg/min infusion rate, prolongation

Table 1

NUMBER OF RANDOMIZED PATIENTS WHO HAD PRIMARY ENDPOINTS

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)	Dose Response p-Value
Patients with events	227 (10.8%)	89 (12.8%)	79 (11.5%)	59 (8.3%)	0.009
% reduction vs. placebo			10.4%	34.8%	
p-value vs. placebo			0.428	0.008	

The analysis of primary endpoint components is shown in Table 2. Death was relatively rare and occurred with similar frequency in each group. The greatest dose-response effects were seen in the MI (p=0.013) and urgent intervention (p=0.003) event rates. Patients who received the bolus plus infusion treatment had a 39.4% reduction in the incidence of MI (p=0.014, pairwise vs placebo) and a 49.1% reduction in the incidence of urgent intervention (p=0.003, pairwise vs placebo).

Table 2

NUMBER OF RANDOMIZED PATIENTS WHO HAD PRIMARY ENDPOINTS BY COMPONENT[a]

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)	Dose Response p-Value
Death	33 (1.6%)	12 (1.7%)	9 (1.3%)	12 (1.7%)	0.964
% reduction vs. placebo			24.8%	1.6%	
p-value vs. placebo			0.511	0.963	
MI	140 (6.7%)	60 (8.6%)	43 (6.2%)	37 (5.2%)	0.013
% reduction vs. placebo			28.2%	39.4%	
p-value vs. placebo			0.091	0.014	
Urgent intervention	126 (6.0%)	54 (7.8%)	44 (6.4%)	28 (4.0%)	0.003
% reduction vs. placebo			17.2%	49.1%	
p-value vs. placebo			0.300	0.003	

[a]Patients were counted once within a component, but could have been counted in more than one component.

Compared to the placebo group, there was a lower incidence of Q-wave and large non-Q-wave infarctions as well as smaller non-Q-wave infarctions in the bolus plus infusion treatment group, as shown in Table 3.

Table 3

NUMBER OF PATIENTS WITH MI BY TYPE OF MI

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)	Dose Response p-Value
Q-wave	29 (1.4%)	16 (2.3%)	7 (1.0%)	6 (0.8%)	0.020
% reduction vs. placebo			56.2%	63.1%	
p-value vs. placebo			0.090	0.032	
Large non-Q-wave[a]	68 (3.2%)	28 (4.0%)	19 (2.7%)	21 (3.0%)	0.265
% reduction vs. placebo			32.0%	26.3%	
p-value vs. placebo			0.235	0.310	
Small non-Q-wave	43 (2.0%)	16 (2.3%)	17 (2.4%)	10 (1.4%)	0.239
% reduction vs. placebo			-6.4%	38.6%	
p-value vs. placebo			0.862	0.240	
All MI[b]	140 (6.7%)	60 (8.6%)	43 (6.2%)	37 (5.2%)	0.011
% reduction vs. placebo			28.2%	39.4%	
p-value vs. placebo			0.101	0.015	

[a] Enzymes ≥5x upper normal.
[b] p-values do not match Table 2 because logrank statistics were used there while Chi-square statistics were used here.

The primary endpoint component with the most marked reduction in event rates with bolus plus infusion treatment was urgent PTCA (81.0% reduction from 4.5% in the placebo groups to 0.9% in the bolus plus infusion treatment group, $p<0.001$). The ischemic events that led to urgent PTCA were characterized by prolonged periods of chest pain with ECG changes suggesting that these events were of serious nature. As shown in Figure 1, placebo-treated patients began experiencing ischemic events requiring urgent repeat PTCA within the first hour after the randomization, and continued to have events over the first 48 hours. Patients treated with the bolus only regimen did not experience events in the first 4 hours following the randomization, but subsequently followed a pattern similar to that seen in placebo-treated patients. Based upon the results of Phase I and II studies the 4 to 6 hour time period after the bolus dose, when ischemic events began to occur in the bolus treatment group, corresponds to the recovery of platelet aggregation to approximately 50% of baseline. The patients receiving the bolus plus infusion regimen had fewer events; these events did not begin until approximately 11 hours after randomization and the event rate quickly achieved a plateau. These results

Table 84

NUMBER OF PATIENTS WHO HAD URGENT INTERVENTION BY COMPONENT[a]

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)	Dose Response p-Value
Urgent PTCA	62 (3.0%)	31 (4.5%)	25 (3.7%)	6 (0.9%)	< 0.001
% reduction vs placebo			17.1%	81.0%	
p-value vs placebo			0.410	< 0.001	
Urgent CABG	58 (2.8%)	25 (3.6%)	16 (2.3%)	17 (2.4%)	0.177
% reduction vs placebo			35.9%	33.2%	
p-value vs placebo			0.157	0.194	
Stent	20 (1.0%)	4 (0.6%)	12 (1.7%)	4 (0.6%)	0.975
% reduction vs placebo			-200.7%	1.7%	
p-value vs placebo			0.045	0.981	
IABP	2 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0.992
% reduction vs placebo			100%	2.8%	
p-value vs placebo			0.317	0.991	

[a] Patients were counted once within a component, but could have been counted in more than one component.

The effectiveness of bolus plus infusion treatment in preventing urgent intervention is further examined as a function of time in Figure 47. These Kaplan-Meier curves show that a smaller percentage of patients in the bolus plus infusion treatment group had an urgent intervention both during the first day following randomization and throughout the 30-day follow-up period. Because the urgent interventions prevented by bolus plus infusion were urgent PTCA and urgent CABG, these are discussed in fuller detail in the following two sections.

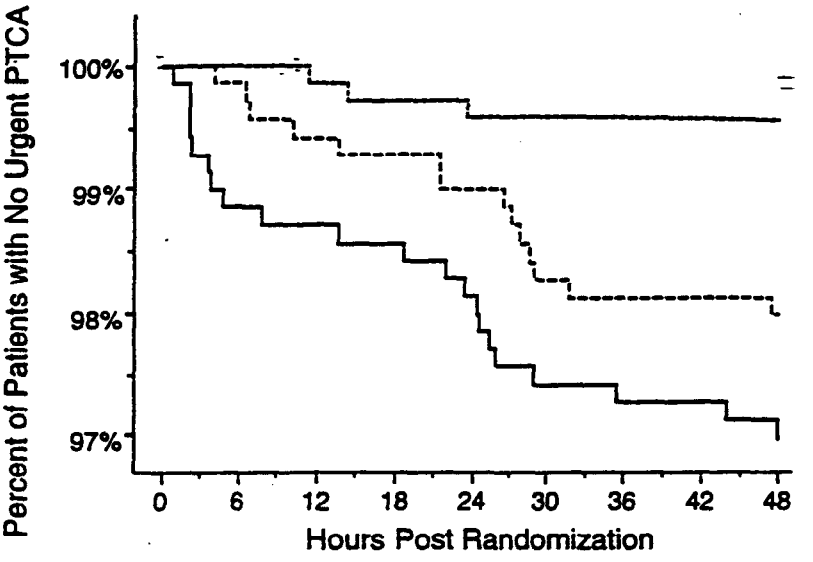


Figure 48 Kaplan Meier plot of Urgent PTCA Event Rates; 0 to 48 Hours After Treatment.

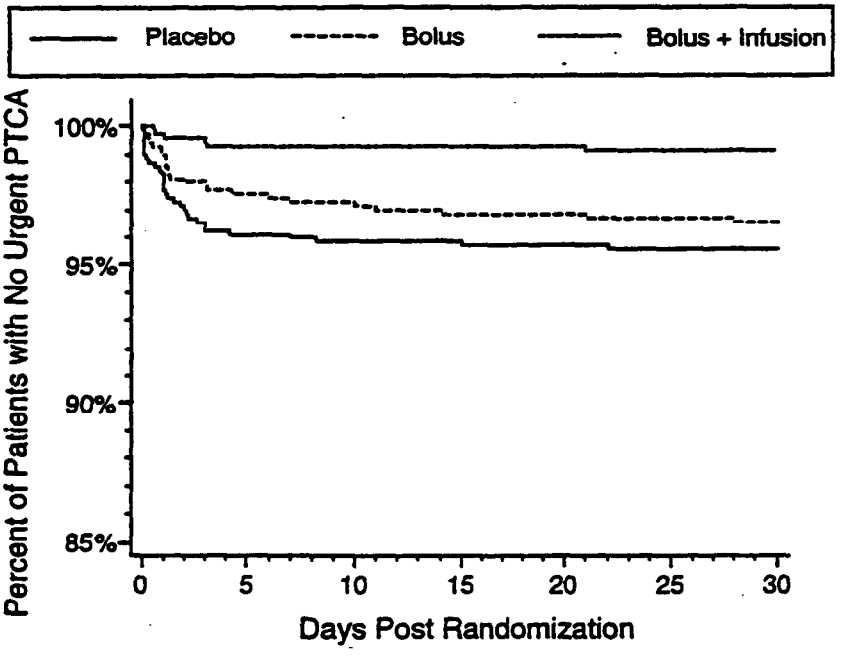


Figure 49 Kaplan Meier plot of Urgent PTCA Event Rates; 0 to 30 Days After Treatment.

There is also a suggestion from these data that bolus plus infusion treatment not only reduces the incidence of the recurrent ischemic events, but when urgent PTCA is necessary, bolus plus infusion treatment may reduce the incidence of new ischemic events.

Table 85

CHARACTERIZATION OF ISCHEMIA IN PATIENTS WITH URGENT PTCA DURING HOSPITALIZATION[a]

	Total	Placebo	Bolus	Bolus + Infusion
Pts with urgent PTCA during index hospitalization	48	25	18	5
Number of ischemic episodes				
0	2 (4.2%)	2 (8.0%)	0 (0.0%)	0 (0.0%)
1	29 (60.4%)	16 (64.0%)	10 (55.6%)	3 (60.0%)
2	10 (20.8%)	3 (12.0%)	5 (27.8%)	2 (40.0%)
≥3	7 (14.6%)	4 (16.0%)	3 (16.7%)	0 (0.0%)
Time of onset[b]				
Pts with time measured	44	22	17	5
Median (hr)	10.8	9.8	11.4	11.0
Interquartile range (hr)	(2.0, 21.1)	(1.3, 21.9)	(3.1, 20.2)	(8.9, 19.3)
Range (hr)	(0.1,195.3)	(0.1,195.3)	(1.6, 25.6)	(4.1, 50.1)
Maximum duration[c]				
Pts with duration measured	38	20	13	5
Median (min)	113.0	113.0	75.0	120.0
Interquartile range (min)	(50.0,165.0)	(67.5,174.5)	(50.0,140.0)	(70.0,170.0)
Range (min)	(10.0,570.0)	(15.0,570.0)	(10.0,225.0)	(30.0,300.0)
Pts with ECG changes[d]	28 (58.3%)	18 (72.0%)	8 (44.4%)	2 (40.0%)
Pts with medication administered	41 (85.4%)	22 (88.0%)	14 (77.8%)	5 (100.0%)
Nitroglycerin	39 (81.3%)	21 (84.0%)	13 (72.2%)	5 (100.0%)
IV Nitroglycerin	28 (58.3%)	14 (56.0%)	10 (55.6%)	4 (80.0%)
SL Nitroglycerin	27 (56.3%)	16 (64.0%)	8 (44.4%)	3 (60.0%)
Calcium channel blocker	1 (2.1%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
Beta blocker	3 (6.3%)	1 (4.0%)	2 (11.1%)	0 (0.0%)
Morphine	14 (29.2%)	8 (32.0%)	5 (27.8%)	1 (20.0%)
Other medication	14 (29.2%)	9 (36.0%)	5 (27.8%)	0 (0.0%)

[a] Ischemic episodes reported after the index PTCA and prior to the urgent (repeat) PTCA.
[b] The elapsed time in hours from the end of the index PTCA to the first ischemic episode.
[c] The maximum duration in minutes among all ischemic episodes reported.
[d] Ischemia with ST elevation or depression.

Table 86

CHARACTERISTICS AND SUBSEQUENT COMPLICATIONS OF PATIENTS WITH URGENT PTCA DURING INDEX HOSPITALIZATION

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)
Pts with urgent PTCA	62	31	25	6
Pts with urgent PTCA during index hospitalization	48 (77.4%)	25 (80.6%)	18 (72.0%)	5 (83.3%)
Pts with pre-PTCA thrombus	23 (47.9%)	15 (60.0%)	8 (44.4%)	0 (0.0%)
Pts with IC thrombolytics used in-cath lab	7 (14.6%)	5 (20.0%)	2 (11.1%)	0 (0.0%)
Pts with PTCA success[a]	35 (72.9%)	18 (72.0%)	13 (72.2%)	4 (80.0%)
Pts with complications and transfusions				
Death	4 (8.3%)	3 (12.0%)	1 (5.6%)	0 (0.0%)
MI	4 (8.3%)	2 (8.0%)	2 (11.1%)	0 (0.0%)
CABG	7 (14.6%)	4 (16.0%)	3 (16.7%)	0 (0.0%)
PTCA	2 (4.2%)	1 (4.0%)	1 (5.6%)	0 (0.0%)
Stent Placement	5 (10.4%)	2 (8.0%)	3 (16.7%)	0 (0.0%)
Heart Failure[b]	4 (8.3%)	4 (16.0%)	0 (0.0%)	0 (0.0%)
Thrombocytopenia	6 (12.5%)	4 (16.0%)	2 (11.1%)	0 (0.0%)
Platelet transfusion	6 (12.5%)	4 (16.0%)	2 (11.1%)	0 (0.0%)

[a] Success is defined as reduction of luminal narrowing <50%.
[b] Includes patients who had heart failure reported as an adverse event or had Killip Class >2

Urgent CABG

The urgent CABG event rate was 2.4% in the bolus plus infusion treatment group, 2.3% in the bolus treatment group, and 3.6% in the placebo treatment group. The majority of the urgent CABGs occurred within 1 day after randomization in all three treatment groups.

Table 87 contains the characteristics and subsequent complications of the patients who had urgent CABG during the index hospitalization. Fifty-six (96.6%) of the 58 patients

events in patients with other high risk strata was observed in the bolus plus infusion treatment group (p=0.125 vs placebo).

Table 89

PRIMARY ENDPOINT EVENT RATES BY RISK STATUS

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with MI or unstable angina	893	288	306	299	
Pts with events	94 (10.6%)	37 (12.8%)	36 (12.0%)	21 (7.0%)	0.025
% reduction vs placebo			6.9%	45.3%	
p-value vs placebo			0.686	0.022	
Pts with other high risk strata	1206	408	389	409	
Pts with events	133 (11.0%)	52 (12.7%)	43 (11.1%)	38 (9.3%)	0.125
% reduction vs placebo			13.2%	27.1%	
p-value vs placebo			0.478	0.125	

Pre-PTCA Thrombus

Patients were divided into two groups according to whether or not a thrombus was observed on their angiogram immediately prior to the index PTCA (not the diagnostic angiogram if it was done earlier). Table 90 displays the analysis of the primary endpoint within the two groups for only those patients who had an index PTCA attempted. The presence of a thrombus was unknown for 17 patients; they were included in the no thrombus group. The event rate in patients with thrombus was slightly lower than the event rate in patients without thrombus or thrombus unknown. In patients with a thrombus, bolus plus infusion treatment was associated with fewer events (49.3% reduction, p=0.042 vs placebo). Bolus plus infusion treatment was also associated with fewer events in patients with no thrombus or thrombus unknown (34.4% reduction, p=0.029 vs placebo).

6 month eff cac tables

TABLE 3.2
NUMBER OF RANDOMIZED PATIENTS WHO HAD DEATH, MI, OR REVASCULARIZATION[a] WITHIN 6 MONTHS OF STUDY ENTRY

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts randomized	2099	696	695	708	
Pts evaluated from Day 0[b]	2099	696	695	708	
Pts with events	654 (31.5%)	241 (35.1%)	224 (32.6%)	189 (27.0%)	0.001
% reduction vs placebo			7.1%	22.9%	
p-value vs placebo			0.276	0.001	
Pts evaluated after Day 2[c]	1863	606	618	639	
Pts with events	419 (22.9%)	151 (25.4%)	148 (24.3%)	120 (19.2%)	0.007
% reduction vs placebo			4.4%	24.6%	
p-value vs placebo			0.588	0.007	
Pts evaluated after 30-day follow-up[d]	1728	549	580	599	
Pts with events	313 (18.3%)	105 (19.3%)	117 (20.3%)	91 (15.3%)	0.071
% reduction vs placebo			-5.2%	20.6%	
p-value vs placebo			0.650	0.070	

[a] Revascularization includes any PTCA (urgent and non-urgent), any CABG (urgent and non-urgent), any intracoronary stent (only in the 30-day follow-up period), and any endpoint IABP (only in the 30-day follow-up period).
[b] Patients who were evaluated from Day 0 through the 6-month follow-up.
[c] Patients who were evaluated from Day 3 through the 6-month follow-up. Excludes patients experiencing death, MI, or revascularization from Day 0 through Day 2.
[d] Patients who were evaluated after 30-day follow-up through 6-month follow-up. Excludes patients experiencing death, MI, or revascularization from Day 0 through 30-day follow-up.

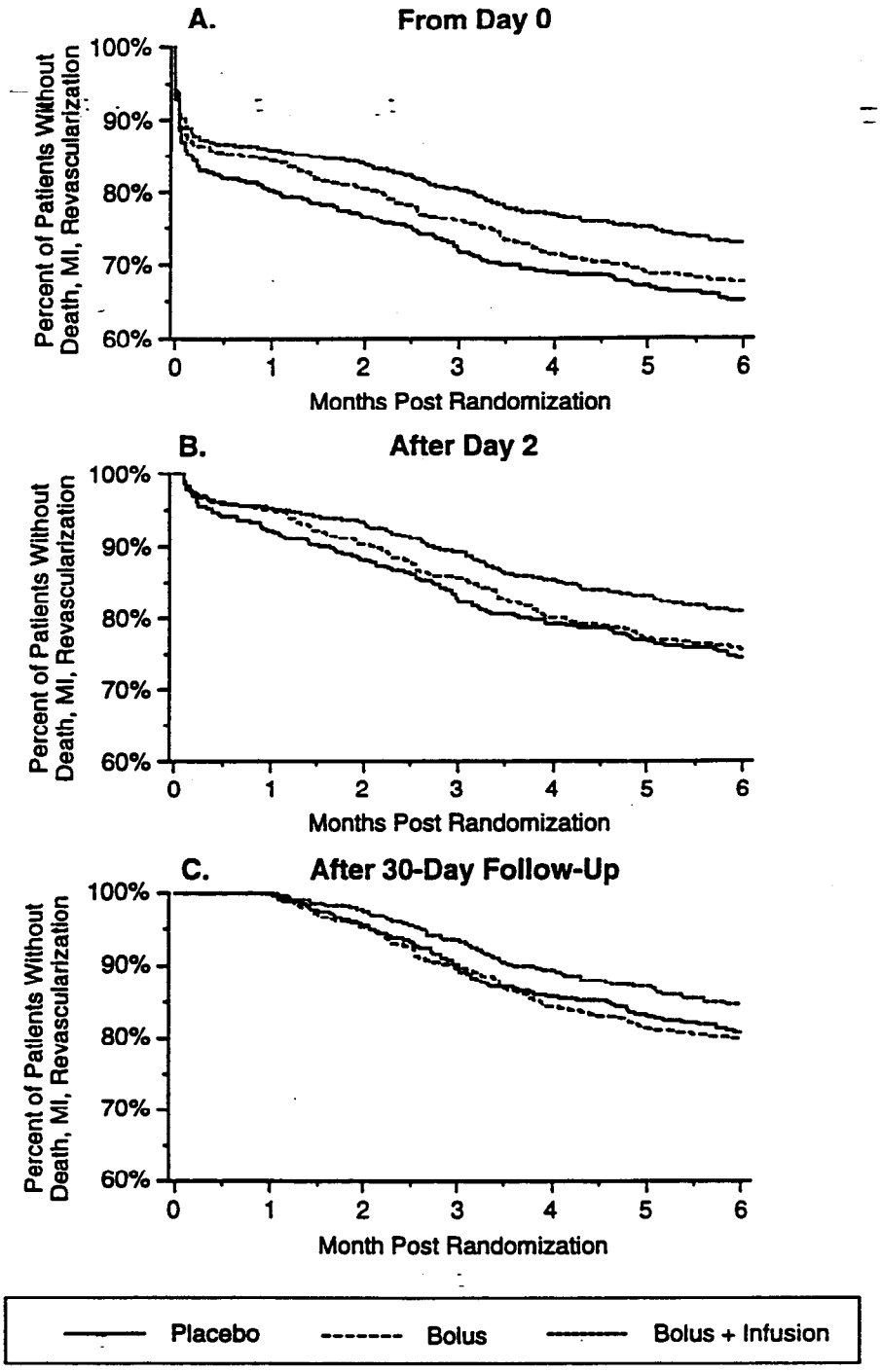


Figure 3.1. Kaplan-Meier event rates for death, MI and revascularization. Panel A represents all patients. Panel B includes patients followed after study Day 2 not experiencing death, MI, or revascularization on study Days 0, 1, or 2. Panel C includes patients followed after the initial 30-day follow-up period not experiencing death, MI, or revascularization during the initial 30-day follow-up period.

Table 3.5 presents the extension of the primary endpoint for the 30-day follow-up (death, MI, urgent intervention) to the 6-month time period. Procedures include PTCA, CABG and during the 30-day follow-up only, stent and IABP. This eliminates approximately half of the endpoints presented in Tables 3.2 and 3.3. For the entire 6-month follow-up, there was a 30.4% reduction in events from 17.6% in the placebo group to 12.3% in the bolus plus infusion group (p=0.006, pairwise). The observed rate of death, MI or urgent intervention after the 30-day follow-up was 22.5% lower in the bolus plus infusion group (4.3%) than in the placebo group (5.5%), however, smaller numbers of events were observed making treatment comparisons non-definitive (pairwise p=0.351). Figure 3.3 shows that the initial 30-day benefit observed in the reduction of the primary endpoint with bolus plus infusion treatment vs. placebo treatment was maintained over the entire 6-month follow-up period.

TABLE 3.5
NUMBER OF RANDOMIZED PATIENTS WHO HAD DEATH, MI, OR URGENT INTERVENTION WITHIN 6 MONTHS OF STUDY ENTRY[a]

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts randomized	2099	696	695	708	
Pts evaluated from Day 0	2099	696	695	708	
Pts with events	322 (15.5%)	121 (17.6%)	115 (16.7%)	86 (12.3%)	0.007
% reduction vs placebo			5.2%	30.4%	
p-value vs placebo			0.651	0.006	
Pts evaluated after Day 2	1915	623	631	661	
Pts with events	139 (7.4%)	48 (7.9%)	52 (8.4%)	39 (6.0%)	0.204
% reduction vs placebo			-5.6%	24.3%	
p-value vs placebo			0.752	0.197	
Pts evaluated after 30-day follow-up	1839	595	607	637	
Pts with events	95 (5.2%)	32 (5.5%)	36 (6.0%)	27 (4.3%)	0.357
% reduction vs placebo			-8.8%	22.5%	
p-value vs placebo			0.679	0.351	

[a] This table extends the analysis of the 30-day primary endpoint of death, MI and urgent intervention (PTCA, CABG, stent, IABP) by adding follow-up for death, MI, urgent PTCA and urgent CABG from the end of the 30-day follow-up period through 6 months.

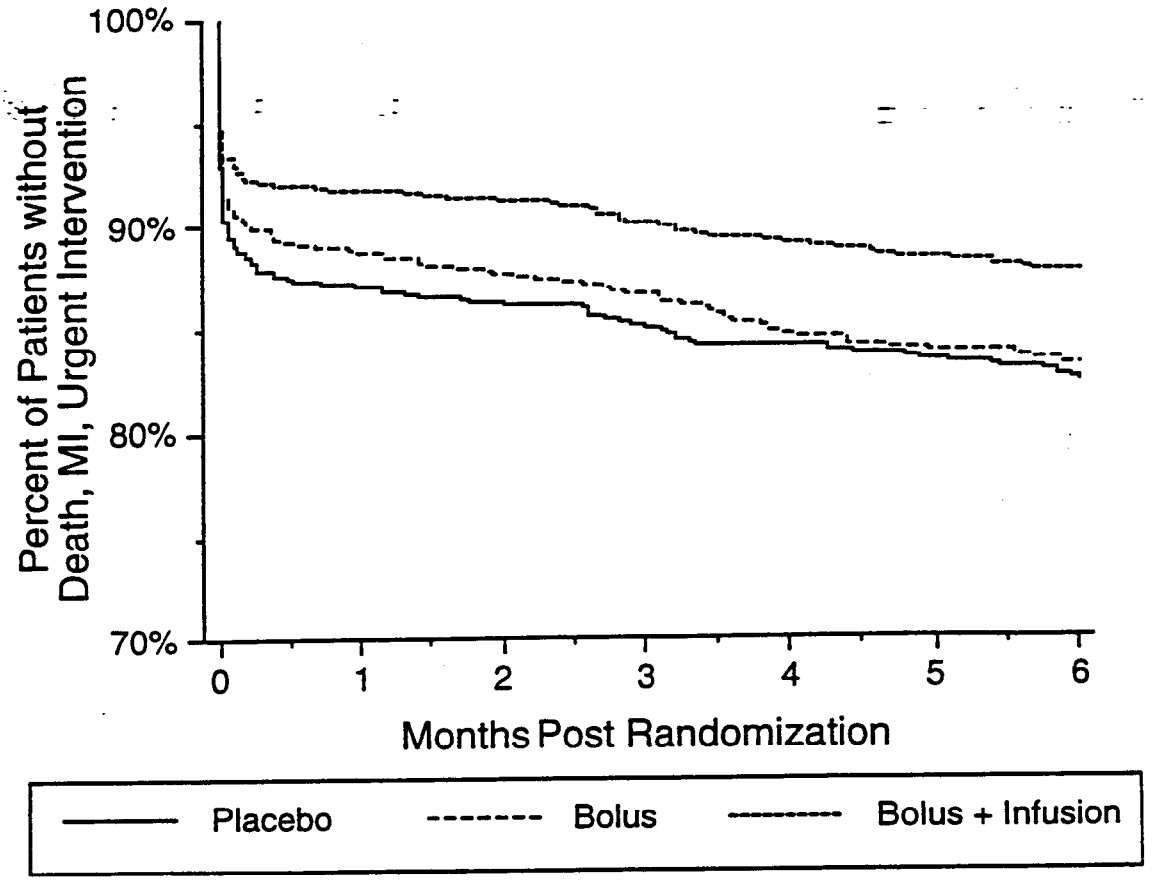


Figure 3.3. Kaplan-Meier event rates for death, MI, and urgent intervention through 6 months.

3.1.3 Component Endpoints

3.1.3.1 Death

Table 3.6 and Figure 3.4 show that no differences in mortality were observed between treatment groups in the 6-month follow-up period. Of the 2099 patients randomized, 63 (3.0%) died during the 6-month follow-up period, 23 (3.4%) in the placebo group, 18 (2.6%) in the bolus group, and 22 (3.1%) in the bolus plus infusion group. Of the 22 deaths that occurred during 6-month follow-up among bolus plus infusion-treated patients, 3 patients were randomized, but not treated.

TABLE 3.13

NUMBER OF PATIENTS WITH INITIALLY SUCCESSFUL PTCA WHO HAD PTCA, CABG, STENT, OR ENDPOINT IABP FOR AN ARTERY TREATED IN THE INITIAL PTCA WITHIN 6 MONTHS OF STUDY ENTRY

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with successful index PTCA	1882	628	627	627	
Pts evaluated from Day 0	1882	628	627	627	
Pts with PRA procedures	363 (20.0%)	135 (22.3%)	128 (21.0%)	100 (16.5%)	0.007
% reduction vs placebo			5.9%	26.2%	
p-value vs placebo			0.569	0.007	
Pts evaluated after Day 2	1825	600	605	620	
Pts with PRA procedures	312 (17.7%)	109 (19.0%)	109 (18.6%)	94 (15.7%)	0.135
% reduction vs placebo			2.2%	17.4%	
p-value vs placebo			0.881	0.133	
Pts evaluated after 30-day follow-up	1739	566	579	594	
Pts with PRA procedures	274 (16.0%)	94 (16.9%)	95 (16.6%)	85 (14.4%)	0.265
% reduction vs placebo			1.6%	14.5%	
p-value vs placebo			0.940	0.264	

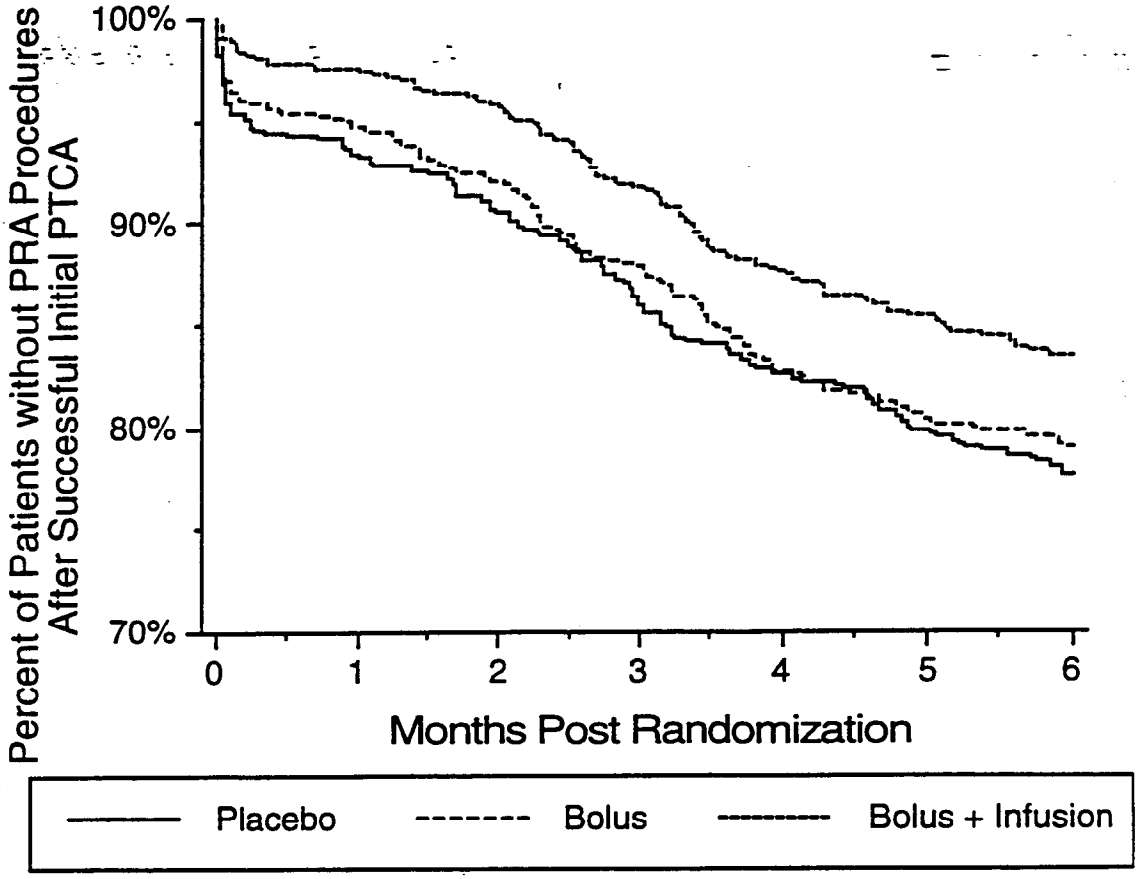


Figure 3.11. Kaplan-Meier event rates through 6 months for PRA procedures in patients with initially successful PTCA.

TABLE 3.14

NUMBER OF RANDOMIZED PATIENTS WHO HAD DEATH, MI, OR REVASCULARIZATION WITHIN 6 MONTHS OF STUDY ENTRY BY MI OR UNSTABLE ANGINA AT STUDY ENTRY VS. PATIENTS WITH OTHER HIGH RISK CHARACTERISTICS

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Patients evaluated from Day 0	2099	696	695	708	
Pts with MI or unstable angina[a]	893	288	306	299	
Pts with events	259 (29.3%)	95 (33.4%)	88 (29.0%)	76 (25.8%)	0.037
% reduction vs placebo			13.4%	22.9%	
p-value vs placebo			0.225	0.038	
Pts with other high risk strata[b]	1206	408	389	409	
Pts with events	395 (33.2%)	146 (36.2%)	136 (35.4%)	113 (28.0%)	0.013
% reduction vs placebo			2.1%	22.8%	
p-value vs placebo			0.732	0.012	

[a] Patients with stratification criteria A1 (unstable angina at rest), A2 (recurrent unstable angina), A3 (post infarction angina), B1 (direct PTCA for MI), B2 (rescue PTCA), C5 (PTCA of infarct related lesion within 7 days of MI) and CEC-determined acute MI evolving at the time of enrollment.

[b] Patients with stratification criteria other than those listed in footnote a.

TABLE 3.16
NUMBER OF RANDOMIZED PATIENTS WHO HAD DEATH, MI, OR REVASCULARIZATION AFTER 30-DAY FOLLOW-UP THROUGH 6 MONTHS BY MI OR UNSTABLE ANGINA AT STUDY ENTRY VS. PATIENTS WITH OTHER HIGH RISK CHARACTERISTICS

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Patients evaluated after 30-day follow-up	1728	549	580	599	
Pts with MI or unstable angina[a]	739	225	258	256	
Pts with events	117 (16.0%)	37 (16.7%)	42 (16.4%)	38 (15.0%)	0.630
% reduction vs placebo			1.5%	10.1%	
p-value vs placebo			0.965	0.636	
Pts with other high risk strata[b]	989	324	322	343	
Pts with events	196 (20.0%)	68 (21.1%)	75 (23.4%)	53 (15.6%)	0.061
% reduction vs placebo			-10.9%	26.3%	
p-value vs placebo			0.475	0.056	

[a] Patients with stratification criteria A1 (unstable angina at rest), A2 (recurrent unstable angina), A3 (post infarction angina), B1 (direct PTCA for MI), B2 (rescue PTCA), C5 (PTCA of infarct related lesion within 7 days of MI) and CEC-determined acute MI evolving at the time of enrollment.

[b] Patients with stratification criteria other than those listed in footnote a.

3.2.2 Thrombus vs. No Thrombus at Baseline

Another prespecified analysis in the 30-day study report compared event rates between patients with visible thrombus at entry vs. those without visible thrombus. Table 3.17 shows that 6-month follow-up results were consistent for patients with thrombus at baseline as compared to those without. The post study Day 2 and post 30-day follow-up results are comparable and are included in Attachment 2 as Tables 3 and 4, respectively.

3.2.7 Procedure Characteristics

Table 3.33 shows rates of the composite endpoint of death, MI and revascularization by the number of segments treated in the initial treatment PTCA among patients who had PTCA attempted. There was no difference in event rates among patients with more than one segment treated. Among patients with a single segment treated, there was a 34.3% reduction in the rate of patients experiencing death, MI, or revascularization during the 6-month follow-up from 33.4% in placebo group to 22.0% in the bolus plus infusion group (p=<0.001, pairwise). Figure 3.14 shows the Kaplan-Meier event rates in these two groups over time. The post Day 2 and post-30-day follow-up time periods are presented for these subgroups in Attachment 2 in Tables 9 and 10.

TABLE 3.33
NUMBER OF PATIENTS WITH PTCA ATTEMPTED WHO HAD DEATH, MI, OR REVASCULARIZATION WITHIN 6 MONTHS OF STUDY ENTRY BY NUMBER OF SEGMENTS TREATED

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with PTCA attempted evaluated from Day 0	2058	682	687	689	
Pts with events	632 (31.1%)	233 (34.6%)	220 (32.4%)	179 (26.3%)	0.001
% reduction vs placebo			6.5%	23.9%	
p-value vs placebo			0.317	0.001	
Number of segments treated					
1 segment	1398	458	465	475	
Pts with events	389 (28.2%)	151 (33.4%)	135 (29.5%)	103 (22.0%)	<0.001
% reduction vs placebo			11.9%	34.3%	
p-value vs placebo			0.177	<0.001	
> 1 segment	660	224	222	214	
Pts with events	243 (37.2%)	82 (37.1%)	85 (38.4%)	76 (36.1%)	0.739
% reduction vs placebo			-3.7%	2.6%	
p-value vs placebo			0.889	0.749	

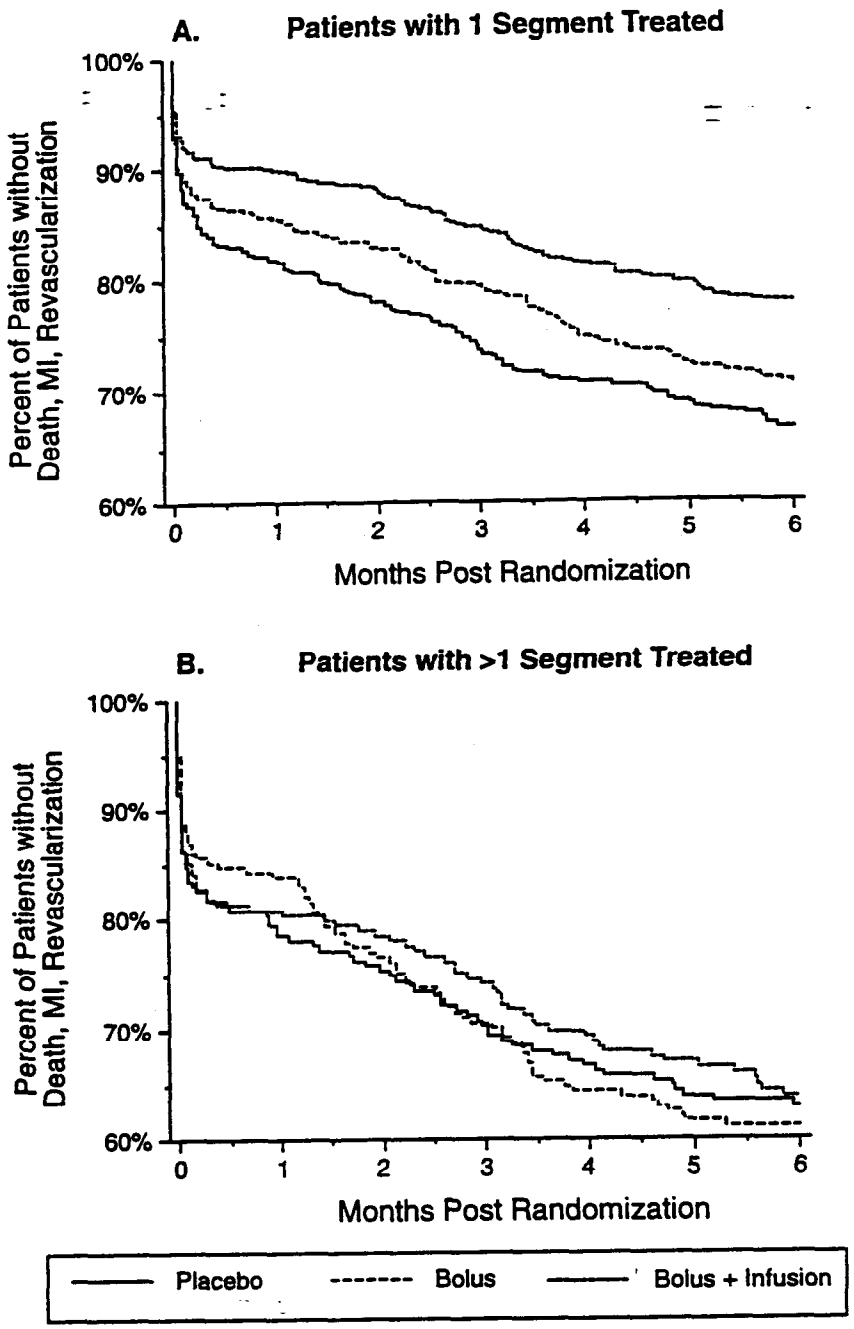


Figure 3.14. Kaplan-Meier event rates for death, MI or revascularization by number of segments treated in treatment PTCA.

TABLE 3.34

NUMBER OF PATIENTS WITH SUCCESSFUL INITIAL PTCA WHO HAD DEATH, MI, OR REVASCULARIZATION WITHIN 6 MONTHS OF STUDY ENTRY BY DURATION OF TREATMENT PTCA

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with successful index PTCA evaluated from Day 0	1882	628	627	627	
Pts with known duration of PTCA	1842	610	621	611	
<40 min	625	206	207	212	
Pts with events	150 (24.3%)	56 (27.7%)	54 (26.3%)	40 (19.2%)	0.043
% reduction vs placebo			4.9%	30.8%	
p-value vs placebo			0.706	0.042	
40 - 70 min	617	190	200	227	
Pts with events	155 (25.6%)	59 (31.6%)	48 (24.5%)	48 (21.5%)	0.012
% reduction vs placebo			22.5%	32.0%	
p-value vs placebo			0.103	0.011	
>70 min	600	214	214	172	
Pts with events	209 (35.2%)	77 (36.4%)	79 (37.2%)	53 (31.3%)	0.286
% reduction vs placebo			-2.2%	14.1%	
p-value vs placebo			0.883	0.264	
Univariate duration p-value	< 0.001	0.033	< 0.001	< 0.001	

model and the adjusted p-values were obtained using models that included age, gender, and height as covariates which could potentially influence the apparent association of weight with events. As shown in these tables, weight appears to be associated with primary endpoint event rates in the bolus plus infusion and bolus treatment groups for all primary endpoint components, except urgent CABG. There is no apparent association between weight and primary endpoint event rates in the placebo treatment group, except endpoint MI.

TABLE 6.3.13
PRIMARY ENDPOINT EVENT RATES BY WEIGHT

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with weight measurement	2097	696	694	707	
Pts with weight ≤75 kg	653	197	231	225	
Pts with events	88 (13.5%)	26 (13.2%)	34 (14.7%)	28 (12.4%)	0.813
% reduction vs placebo			-11.5%	5.7%	
p-value vs placebo			0.646	0.827	
Pts with weight 75.1 to 89.9 kg	737	234	243	260	
Pts with events	83 (11.4%)	31 (13.2%)	33 (13.9%)	19 (7.3%)	0.039
% reduction vs placebo			-4.7%	44.8%	
p-value vs placebo			0.936	0.034	
Pts with weight ≥90 kg	707	265	220	222	
Pts with events	56 (7.9%)	32 (12.1%)	12 (5.5%)	12 (5.4%)	0.006
% reduction vs placebo			54.8%	55.2%	
p-value vs placebo			0.014	0.013	
Unadjusted weight dose response p-value	0.002	0.426	0.005	0.026	
Adjusted p-value[a]	< 0.001	0.643	<0.001	0.022	

[a] Adjusted = Adjusted for age, gender, and height.

There were 620 patients who received <10,000 units of heparin. This group includes 21 patients who did not receive a heparin bolus dose in the cath lab, but did receive a continuous heparin infusion. Thirty-one patients had PTCA attempted but no heparin data; therefore, they were not included in any heparin subgroups in this table. Appendix H indicates the patients who did not receive a heparin bolus dose. There was a consistent trend relative to placebo in reducing primary endpoint events across all initial heparin doses in the bolus plus infusion treatment group.

TABLE 6.3.25
PRIMARY ENDPOINT EVENT RATES
BY INITIAL HEPARIN BOLUS DOSE IN CATH LAB

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with PTCA attempted	2058	682	687	689	
Pts receiving <10,000 U[a]	620	203	214	203	
Pts with events	55 (8.9%)	23 (11.3%)	21 (10.0%)	11 (5.4%)	0.040
% reduction vs placebo			11.4%	52.2%	
p-value vs placebo			0.624	0.036	
Pts receiving 10,000 U	1035	350	342	343	
Pts with events	120 (11.6%)	50 (14.3%)	37 (10.8%)	33 (9.6%)	0.063
% reduction vs placebo			24.3%	32.7%	
p-value vs placebo			0.181	0.068	
Pts receiving >10,000 U	372	123	119	130	
Pts with events	41 (11.0%)	13 (10.6%)	20 (16.9%)	8 (6.2%)	0.266
% reduction vs placebo			-59.4%	41.8%	
p-value vs placebo			0.174	0.218	

[a] Includes patients who did not receive a heparin bolus dose in cath lab, but did receive heparin infusion.

Table 6.3.26 shows the primary endpoint event rates by total heparin bolus dose in the cath lab. As in Table 6.3.25, the <10,000 units of heparin category includes 21 patients who did not receive a heparin bolus dose in the cath lab, and the 31 patients who had PTCA attempted but no heparin data are excluded. Trends in event rates were similar to those seen with the initial heparin bolus dose. This might have been expected based on the fact that the initial bolus was large relative to subsequent bolus doses, and often only a single bolus dose was given in the cath lab.

Interestingly, at the doses used in this study, there was no observed relationship between either initial or total heparin bolus dose and the occurrence of primary endpoint events in any of the treatment groups. This suggests (particularly in the placebo treatment group) that heparin did

not prevent primary endpoint events. In fact, the primary endpoint event rate was lowest in patients in the bolus plus infusion treatment group who received <10,000 units of heparin by bolus in the cath lab.

TABLE 6.3.26
PRIMARY ENDPOINT EVENT RATES
BY TOTAL HEPARIN BOLUS DOSE IN CATH LAB

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with PTCA attempted	2058	682	687	689	
Pts receiving <10,000 U[a]	346	106	119	121	
Pts with events	28 (8.1%)	11 (10.4%)	12 (10.1%)	5 (4.1%)	0.087
% reduction vs placebo			2.6%	60.2%	
p-value vs placebo			0.960	0.073	
Pts receiving 10,000 U	717	220	249	248	
Pts with events	72 (10.1%)	22 (10.0%)	29 (11.9%)	21 (8.5%)	0.565
% reduction vs placebo			-18.7%	15.3%	
p-value vs placebo			0.589	0.575	
Pts receiving >10,000-14,000 U	439	141	154	144	
Pts with events	46 (10.5%)	22 (15.6%)	11 (7.1%)	13 (9.0%)	0.081
% reduction vs placebo			54.2%	42.2%	
p-value vs placebo			0.027	0.102	
Pts receiving >14,000 U	525	209	153	163	
Pts with events	70 (13.3%)	31 (14.8%)	26 (17.0%)	13 (8.0%)	0.081
% reduction vs placebo			-14.8%	46.2%	
p-value vs placebo			0.601	0.051	

[a] Includes patients who did not receive a heparin bolus dose in cath lab, but did receive heparin infusion.

Because the relationship between heparin dose and the extent of anticoagulation achieved is complex and unpredictable, ACTs in the cath lab were also examined as a more direct measure of the relationship between the degree of anticoagulation and the occurrence of the primary endpoint. Tables 6.3.27, 6.3.28, and 6.3.29 show the primary endpoint event rate by initial, minimum, and maximum ACT in the cath lab. There was a consistent reduction in events in the bolus plus infusion treatment group compared with the placebo treatment group in all ACT categories. This reduction was most marked in the maximum ACT <300 seconds category, where the event rate in the bolus plus infusion treatment group was 4.3% vs 13.5% in the placebo treatment group (pairwise p=0.024). There were also notably fewer patients with primary endpoint events in the

Appendix 3: Safety

IV. Safety data

30 day safety data:

Deaths and strokes

- The numbers of deaths (33) and strokes (hemorrhagic and non-hemorrhagic, S=14) were similar among treatment groups

TABLE 7.2.2
TIMING OF OCCURRENCE, TYPE OF STROKE, AND SURVIVAL STATUS OF PATIENTS WHO HAD STROKE

Patient Number	Treated with Study Agent	Timing of Stroke Relative to Bolus Injection[a]	Hemorrhagic or Non-Hemorrhagic	Survival Status at 30-Day Follow-up
Placebo				
[illegible]	Yes	43.6 h	Hemorrhagic	Dead
[illegible]	Yes	6.9 h	Hemorrhagic	Alive
[illegible]	Yes	1.0 h	Non-hemorrhagic	Alive
[illegible]	Yes	13 d	Non-hemorrhagic	Alive
Bolus				
[illegible]	Yes	60.5 h	Non-hemorrhagic	Dead
[illegible]	Yes	0.1 h	Non-hemorrhagic	Alive
[illegible]	Yes	<1 d	Non-hemorrhagic	Alive
[illegible]	Yes	52.5 h	Non-hemorrhagic	Dead
[illegible]	Yes	3 d	Non-hemorrhagic	Dead
[illegible]	Yes	5.8 h	Hemorrhagic	Alive
Bolus + infusion				
[illegible]	No	0.1 h	Non-hemorrhagic	Dead
[illegible]	No	2.4 h	Hemorrhagic	Dead
[illegible]	Yes	7 d	Hemorrhagic	Dead
[illegible]	Yes	3 d	Non-hemorrhagic	Alive
[illegible]	Yes	11.0 h	Hemorrhagic	Alive

[a] If patient was not treated, the timing of stroke is expressed relative to randomization.

7.3 Bleeding

sole access to the cabinet. In this instance, the original page 6 will not be monitored by the CRA. If the site unblinds the patient because of a serious and unexpected adverse event, the site is requested not to attribute a relationship between the event and the study agent in preparing the Safety Report or the CRF. However, a separate confidential letter describing the event, the circumstances of unblinding, and the identification of the study agent, will be sent directly by the investigator to the Safety and Efficacy Monitoring Committee chairman.

ADVERSE EVENTS RECORDED IN THE CRF

The CRF is designed to capture any deleterious and/or unintended event (including serious and unexpected) which occurs during the conduct of this clinical trial. For purposes of this study, endpoints are not captured or reported as adverse events, but are considered to be clinical events that are recorded separately.

1. Definition

   a. *Bleeding Events*

   Bleeding events are defined as major, minor, or insignificant, employing the Thrombolysis in Myocardial Infarction (TIMI) Study Group criteria for bleeding (Rao *et al.* J Am Coll Card 11:1-11, 1988). Major bleeds are defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin greater than 5 g/dl (or, when hemoglobin is not available, a hematocrit decrease of at least 15%). Bleeding is defined as minor if: 1) it is spontaneous and observed as gross hematuria or hematemesis, or 2) if blood loss is observed, whether spontaneous or nonspontaneous, with hemoglobin decreasing greater than 3 g/dl (or, when hemoglobin is not available, a hematocrit decrease of at least 10%) or 3) a decrease in hemoglobin greater than 4 g/dl (or, when hemoglobin is not available, a hematocrit decrease of at least 12%) with no bleeding site identified despite an effort to find one. Blood loss that is insufficient to meet criteria for minor bleeding is to be considered insignificant. To account for transfusion, the following algorithm will be applied to all patients transfused prior to the determination of major or minor bleeding: (the change in hematocrit/3) + (the number of units of PRBCs transfused) = the change in hemoglobin (Landefeld *et al.* Am J Med 82:703, 1987). Bleeding which meets the above criteria for major and minor bleeding events, but which is judged to be blood loss associated with a surgical procedure will be considered separately from other bleeding.

   b. *Adverse Events Other than Bleeding*

   This trial predefines specific categories of adverse events. These pre-specified categories include:

   - Neurologic
   - Arrhythmia
   - Pump dysfunction
   - Pulmonary/renal
   - Vascular
   - Miscellaneous
   - Other/additional

   The "Other/additional" category includes anything that is not listed in one of the pre-specified categories, and those events within one of the pre-specified categories above that occur more than once.

safety tables

TABLE 7.3.2
NUMBER OF PATIENTS WITH BLEEDING EVENTS[a]

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)	Dose Response p-Value
Pts with major bleeding[b]	222 (10.6%)	46 (6.6%)	77 (11.1%)	99 (14.0%)	< 0.001
% change vs placebo			+67.6%	+111.6%	
p-value vs placebo			0.003	< 0.001	
Pts with minor bleeding[b]	295 (14.1%)	68 (9.8%)	107 (15.4%)	120 (16.9%)	< 0.001
% change vs placebo			+57.6%	+73.5%	
p-value vs placebo			0.002	< 0.001	
Pts with insignificant or no bleeding[b]	1559 (74.3%)	572 (82.2%)	505 (72.7%)	482 (68.1%)	< 0.001
% change vs placebo			-11.6%	-17.2%	
p-value vs placebo			< 0.001	< 0.001	
Pts not evaluated	23 (1.1%)	10 (1.4%)	6 (0.9%)	7 (1.0%)	0.422
% change vs placebo			-39.9%	-31.2%	
p-value vs placebo			0.452	0.475	

[a] Patients with blood loss associated with CABG are included in this table.
[b] Patients who had blood loss in more than one classification are counted only once according to the most severe classification. Patients with blood loss of the same classification on more than one occasion are counted once within that classification.

Table 7.3.3 shows the number of patients with bleeding events which were not associated with CABG. The frequency of major bleeding events not associated with CABG was three-fold higher in the bolus plus infusion treatment group (10.6%) compared with placebo (3.3%); this difference was statistically significant ($p<0.001$). Four patients in the bolus plus infusion treatment group (———————) who had major bleeding events not associated with CABG were randomized but not treated with study agent. A higher rate of major bleeding not associated with CABG was also observed in the bolus treatment group (8.6%, $p<0.001$ vs placebo). A similar relationship among treatment groups was observed in patients with minor bleeding events not associated with CABG although the relative increase in event rate vs placebo was smaller in the two c7E3 Fab treatment groups. Minor bleeding events occurred in 16.8% of the patients in the bolus plus infusion treatment group, 15.5% of the patients in the bolus treatment group and 9.2% of the patients in the placebo treatment group.

TABLE 7.3.3
NUMBER OF PATIENTS WITH BLEEDING EVENTS NOT ASSOCIATED WITH CABG

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + Infusion (n=708)	Dose Response p-Value
Pts with major bleeding[a]	158 (7.5%)	23 (3.3%)	60 (8.6%)	75 (10.6%)	< 0.001
% change vs placebo			+161.2%	+220.6%	
p-value vs placebo			< 0.001	< 0.001	
Pts with minor bleeding[a]	291 (13.9%)	64 (9.2%)	108 (15.5%)	119 (16.8%)	< 0.001
% change vs placebo			+69.0%	+82.8%	
p-value vs placebo			< 0.001	< 0.001	
Pts with insignificant or no bleeding, or blood loss associated with CABG[a]	1627 (77.5%)	599 (86.1%)	521 (75.0%)	507 (71.6%)	< 0.001
% change vs placebo			-12.9%	-16.8%	
p-value vs placebo			< 0.001	< 0.001	
Pts not evaluated	23 (1.1%)	10 (1.4%)	6 (0.9%)	7 (1.0%)	0.422
% change vs placebo			-39.9%	-31.2%	
p-value vs placebo			0.452	0.475	

[a] Patients who had bleeding in more than one classification are counted only once according to the most severe classification. Patients with multiple bleeding events of the same classification are also counted once within that classification.

Table 7.3.4 lists the patient numbers of patients who had major bleeding events not associated with CABG. Patient narratives for each of these patients are in Attachment 10.

received greater than 5 units of packed RBCs or whole blood (8 patients in the bolus plus infusion treatment group, 6 in the bolus treatment group, and 2 in the placebo treatment group). The most common serious or life-threatening event coinciding with major bleeding was hypotension which occurred in more of the c7E3 Fab-treated patients than placebo patients. There was no notable increase in the need for surgical intervention as a consequence of major bleeding in the c7E3 Fab-treated groups. The important consequences associated with bleeding occurred in proportion to the number of patients who had major bleeding in each treatment group, suggesting that if bleeding risk could be lowered, the incidence of these consequences would also decrease.

Table 6

CHARACTERISTICS OF MAJOR BLEEDING EVENTS

	Placebo	Bolus	Bolus + Infusion
Major bleeding[a]	23/696 (3.3%)	60/695 (8.6%)	75/708 (10.6%)
Site of major bleed[b]			
Intracranial	2 (8.7%)	1 (1.7%)	3 (4.0%)[c]
Gross hematuria	1 (4.3%)	4 (6.7%)	4 (5.3%)
Other genitourinary	2 (8.7%)	5 (8.3%)	8 (10.7%)
Hematemesis	0 (0.0%)	5 (8.3%)	11 (14.7%)
Other gastrointestinal	1 (4.3%)	11 (18.3%)	11 (14.7%)
Access sites	17 (73.9%)	42 (71.7%)	54 (72.0%)
Groin	16	43	50
Retroperitoneal	2	2	12
Brachial	0	1	0
Other	1	1	4
Oral	1 (4.3%)	4 (6.7%)	4 (5.3%)
Otic	0 (0.0%)	1 (1.7%)	0 (0.0%)
Other	1 (4.3%)	8 (13.3%)	11 (14.7%)
Decrease in Hct/Hgb only	3(13.0%)	7(11.7%)	11(14.7%)
Transfusions[b]			
RBC/Whole blood	14 (60.9%)	42 (70.0%)	55 (73.3%)
Platelets	2 (8.7%)	10 (16.7%)	10 (13.3%)
Hypotension[b,d]	8 (34.8%)	18 (30.0%)	23 (30.7%)
Surgery intervention for bleeding[b]	6 (26.1%)	12 (20.0%)	5 (6.7%)

[a] Patients may be included for more than one bleeding site or transfusion type. Patients who only had blood loss associated with CABG are not included in this table.
[b] Percentages are based on the number of patients with major bleeding.
[c] Includes one patient randomized but not treated.
[d] Hypotension that was serious, life-threatening, or fatal.

Factors that may influence risk of bleeding

Heparin

- Bolus dose of >10000 units associated with more bleeding
- Total heparin dose of ≥10000 units associated with bleeding
- There is more bleeding in all dose groups with higher ACT levels; bleeding was greater in bolus plus infusion group for all levels of ACT; same observation for APTT

TABLE 7.3.31
NUMBER OF PATIENTS WITH MAJOR BLEEDING EVENTS
BY INITIAL HEPARIN BOLUS DOSE IN CATH LAB

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts receiving heparin[a]	2043	682	676	685	
Pts receiving <10,000 U	627	206	214	207	
Pts with major bleeding	41 (6.5%)	10 (4.9%)	14 (6.5%)	17 (8.2%)	0.168
% change vs placebo			+34.8%	+69.2%	
p-value vs placebo			0.531	0.232	
Pts receiving 10,000 U	1044	353	343	348	
Pts with major bleeding	81 (7.8%)	9 (2.5%)	30 (8.7%)	42 (12.1%)	< 0.001
% change vs placebo			+243.1%	+373.4%	
p-value vs placebo			< 0.001	< 0.001	
Pts receiving >10,000 U	372	123	119	130	
Pts with major bleeding	28 (7.5%)	3 (2.4%)	13 (10.9%)	12 (9.2%)	0.044
% change vs placebo			+347.9%	+278.5%	
p-value vs placebo			0.009	0.031	

[a] Only includes patients who received heparin in the cath lab.

A similar analysis to that shown in Table 7.3.31 was performed using the total dose of heparin administered as a bolus in the cath lab, i.e., including supplemental bolus doses of heparin following the initial bolus dose. In this analysis, shown in Table 7.3.32, patients who received >10,000 units of heparin were further subgrouped as to whether they received >10,000 to 14,000 units of heparin or >14,000 units of heparin. Similar to the

results shown in Table 7.3.31 there was a greater incidence of major bleeding in both c7E3 Fab treatment groups for all intervals of the total heparin bolus dose examined. There was also a trend for higher bleeding event rates as the total bolus dose of heparin increased in patients receiving c7E3 Fab.

TABLE 7.3.32
NUMBER OF PATIENTS WITH MAJOR BLEEDING EVENTS
BY TOTAL HEPARIN BOLUS DOSE IN CATH LAB

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts receiving heparin[a]	2043	682	676	685	
Pts receiving <10,000 U	352	108	119	125	
Pts with major bleeding	20 (5.7%)	4 (3.7%)	6 (5.0%)	10 (8.0%)	0.154
% change vs placebo			+36.1%	+116.0%	
p-value vs placebo			0.751	0.269	
Pts receiving 10,000 U	726	224	250	252	
Pts with major bleeding	49 (6.7%)	2 (0.9%)	22 (8.8%)	25 (9.9%)	< 0.001
% change vs placebo			+885.6%	+1011.1%	
p-value vs placebo			< 0.001	< 0.001	
Pts receiving >10,000-14,000 U	439	141	154	144	
Pts with major bleeding	38 (8.7%)	8 (5.7%)	14 (9.1%)	16 (11.1%)	0.103
% change vs placebo			+60.2%	+95.8%	
p-value vs placebo			0.279	0.135	
Pts receiving >14,000 U	526	209	153	164	
Pts with major bleeding	43 (8.2%)	8 (3.8%)	15 (9.8%)	20 (12.2%)	0.003
% change vs placebo			+156.1%	+218.6%	
p-value vs placebo			0.028	0.003	

[a] Only includes patients who received heparin in the cath lab.

Because prolonged infusion of heparin may expose patients to a greater risk of bleeding, the relationship between major bleeding events and duration of heparin infusion following the index PTCA was examined (Table 7.3.33). The highest percentage of bleeding was observed in patients who received heparin infused for less than 12 hours; this finding may be related to the need to prematurely discontinue heparin infusion in patients who had major bleeding events soon after the index PTCA. The majority of patients (1,544) had heparin infused for 12 to 24 hours and

TABLE 7.3.48
NUMBER OF PATIENTS WITH MAJOR BLEEDING EVENTS
BY ADMINISTRATION OF THROMBOLYTICS

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Pts with thrombolytics given pre-hospitalization[a]	174	55	59	60	
Pts with major bleeding	13 (7.5%)	1 (1.8%)	8 (13.6%)	4 (6.7%)	0.353
% change vs placebo			+645.8%	+266.7%	
p-value vs placebo			0.033	0.366	
Pts with thrombolytics given pre-PTCA[a]	143	45	46	52	
Pts with major bleeding	2 (1.4%)	1 (2.2%)	0 (0.0%)	1 (1.9%)	0.933
% change vs placebo			-100.0%	-13.5%	
p-value vs placebo			0.495	1.000	
Pts undergoing rescue PTCA[b]	22	7	8	7	
Pts with major bleeding	9 (40.9%)	2 (28.6%)	6 (75.0%)	1 (14.3%)	0.595
% change vs placebo			+162.5%	-50.0%	
p-value vs placebo			0.132	1.000	
Pts with thrombolytics given during PTCA	65	23	26	16	
Pts with major bleeding	15 (23.1%)	2 (8.7%)	8 (30.8%)	5 (31.3%)	0.079
% change vs placebo			+253.8%	+259.4%	
p-value vs placebo			0.080	0.101	
Pts with thrombolytics given post-PTCA to discharge	15	7	5	3	
Pts with major bleeding	5 (33.3%)	2 (28.6%)	1 (20.0%)	2 (66.7%)	0.361
% change vs placebo			-30.0%	+133.3%	
p-value vs placebo			1.000	0.500	
Pts with no thrombolytics given	1711	572	562	577	
Pts with major bleeding	123 (7.2%)	16 (2.8%)	42 (7.5%)	65 (11.3%)	< 0.001
% change vs placebo			+167.2%	+302.7%	
p-value vs placebo			< 0.001	< 0.001	

[a] Patients in this category received thrombolytics within 7 days before treatment with study agent. Patients who had rescue PTCA are not included in this category.

[b] Patients who had rescue PTCA received thrombolytics within 12 hours before treatment with study agent.

TABLE 7.3.49
NUMBER OF PATIENTS WITH MAJOR BLEEDING EVENTS
BY GENDER AND WEIGHT

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
All men	1514	506	502	506	
Pts with major bleeding	98 (6.5%)	15 (3.0%)	42 (8.4%)	41 (8.1%)	0.001
% change vs placebo			+182.2%	+173.3%	
p-value vs placebo			< 0.001	< 0.001	
Men ≤75 kg[a]	330	98	114	118	
Pts with major bleeding	34 (10.3%)	3 (3.1%)	12 (10.5%)	19 (16.1%)	0.002
% change vs placebo			+243.9%	+426.0%	
p-value vs placebo			0.057	0.001	
Men >75 kg[a]	1183	408	387	388	
Pts with major bleeding	64 (5.4%)	12 (2.9%)	30 (7.8%)	22 (5.7%)	0.083
% change vs placebo			+163.6%	+92.8%	
p-value vs placebo			0.002	0.078	
All women	585	190	193	202	
Pts with major bleeding	60 (10.3%)	8 (4.2%)	18 (9.3%)	34 (16.8%)	< 0.001
% change vs placebo			+121.5%	+299.8%	
p-value vs placebo			0.066	< 0.001	
Women ≤75 kg[b]	323	99	117	107	
Pts with major bleeding	38 (11.8%)	5 (5.1%)	12 (10.3%)	21 (19.6%)	0.001
% change vs placebo			+103.1%	+288.6%	
p-value vs placebo			0.207	0.002	
Women >75 kg[b]	261	91	76	94	
Pts with major bleeding	22 (8.4%)	3 (3.3%)	6 (7.9%)	13 (13.8%)	0.010
% change vs placebo			+139.5%	+319.5%	
p-value vs placebo			0.303	0.016	

[a] One man did not have weight recorded; this patient was not evaluated for bleeding.
[b] One woman did not have weight recorded; this patient did not have a major bleeding event.

The effect of body weight on the relationship between c7E3 Fab treatment and major bleeding events was further analyzed by examining bleeding rates in patients stratified to the following groups: ≤75 kg (653 patients), >75 to <90 kg (737 patients), and ≥90 kg (707 patients). Table 7.3.50 shows the frequency of major bleeding events according to the three weight categories.

TABLE 7.3.50
NUMBER OF PATIENTS WITH MAJOR BLEEDING EVENTS
BY BODY WEIGHT

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Body Weight					
≤75 kg	653	197	231	225	
Pts with major bleeding	72 (11.0%)	8 (4.1%)	24 (10.4%)	40 (17.8%)	< 0.001
% change vs placebo			+155.8%	+337.8%	
p-value vs placebo			0.016	< 0.001	
>75 to <90 kg	737	234	243	260	
Pts with major bleeding	58 (7.9%)	9 (3.8%)	25 (10.3%)	24 (9.2%)	0.030
% change vs placebo			+167.5%	+140.0%	
p-value vs placebo			0.007	0.019	
≥90 kg	707	265	220	222	
Pts with major bleeding	28 (4.0%)	6 (2.3%)	11 (5.0%)	11 (5.0%)	0.119
% change vs placebo			+120.8%	+118.8%	
p-value vs placebo			0.137	0.138	
Unadjusted weight dose-response p-value	<0.001	0.204	0.036	<0.001	
Adjusted p-value[a]	<0.001	0.195	0.120	0.001	

[a] Adjusted = Adjusted for age, gender, and height.

Table 7.3.51 analyzes the number of patients with major bleeding events by weight for spontaneous major organ and non-spontaneous bleeding. These results demonstrate trends in spontaneous major organ and the non-spontaneous bleeding categories similar to the trends seen in Table 7.3.50. In the bolus plus infusion treatment group, spontaneous major organ bleeding occurred in 12 patients who weighed ≤75 kg, in 2 patients who weighed >75 to <90 kg, and in 3 patients who weighed ≥90 kg compared with 0, 2, and 1 patients, respectively, in the placebo treatment group. Therefore, the increase in spontaneous major organ bleeding in the bolus plus infusion treatment group vs placebo was almost entirely confined to the group of patients

the p-values for the regression analysis at the bottom of the table. These analyses suggest that patients with lower body weights had a greater extent of anticoagulation and this may have contributed in part to the greater incidence of major bleeding events in patients who received c7E3 Fab treatment. It would follow that the toxicity of heparin could be reduced by using lower weight-adjusted doses of heparin when it is used in conjunction with c7E3 Fab.

TABLE 7.3.53
INITIAL ACT IN THE CATH LAB BY BODY WEIGHT[a]

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Body Weight					
≤75 kg					
Pts with ACT measurement	435	127	163	145	
Median (sec)	314	312	303	326	0.403
Interquartile range (sec)	(183,413)	(183,388)	(185,454)	(181,418)	
Range (sec)	(68,>2969)	(99,1500)	(93,1433)	(68,>2969)	
% change vs placebo			-2.9%	+4.5%	
p-value vs placebo			0.094	0.307	
>75 to <90 kg					
Pts with ACT measurement	500	163	169	168	
Median (sec)	289	284	298	277	0.486
Interquartile range (sec)	(193.5,376)	(208,365)	(193,389)	(177.5,386.5)	
Range (sec)	(32,1656)	(32,1656)	(104,883)	(60,791)	
% change vs placebo			+4.9%	-2.6%	
p-value vs placebo			0.725	0.494	
≥90 kg					
Pts with ACT measurement	487	183	149	155	
Median (sec)	262	254	252	272	0.046
Interquartile range (sec)	(181,352)	(180,330)	(177,360)	(186,382)	
Range (sec)	(56,884)	(84,527)	(56,884)	(71,623)	
% change vs placebo			-0.8%	+7.1%	
p-value vs placebo			0.273	0.038	
Regression Analysis					
p-value	< 0.001	< 0.001	0.004	0.008	

[a] This analysis includes only the 2058 patients who had PTCA attempted.

TABLE 7.3.44
NUMBER OF PATIENTS WITH MAJOR BLEEDING EVENTS
BY HISTORY OF GI DISORDER

	Total	Placebo	Bolus	Bolus + Infusion	Dose Response p-Value
Patients with current gastrointestinal disorder	136	45	43	48	
Pts with major bleeding	12(8.8%)	0(0.0%)	5(11.6%)	7(14.6%)	0.014
% change vs placebo			N/A	N/A	
p-value vs placebo			0.025	0.013	
Patients with prior gastrointestinal disorder	520	180	163	177	
Pts with major bleeding	47(9.0%)	6(3.3%)	13(8.0%)	28(15.8%)	<0.001
% change vs placebo			+139.3%	+374.6%	
p-value vs placebo			0.096	<0.001	
Patients without gastrointestinal disorder or gastrointestinal disorder unknown	1443	471	489	483	
Pts with major bleeding	99(6.9%)	17(3.6%)	42(8.6%)	40(8.3%)	0.005
% change vs placebo			+138.0%	+129.4%	
p-value vs placebo			0.002	0.002	

Complication	Placebo	Bolus	Bolus plus infusion
Non-invasive abdominal procedures	1.1%	1.3%	4.5%
GI endoscopy	0.9%	1.7%	1.8%
>5 units RBC transfusion	2 patients	6 patients	8 patients
Hypotension-all	12%	16.5%	21%
Hypotension-reasonably related to c7E3	3.1%	6.8%	7.7%
Hypotension-life threatening	1.5%	3.8%	4.1%

	Primary endpoint event rates		Major bleeding	
Patient characteristic	**Placebo**	**Bolus plus infusion**	**Placebo**	**Bolus plus infusion**
PTCA outcome-success	10.5%	4.5%	3.1%	9.6%
PTCA outcome-failure	38.7%	38.7%	6.5%	19.4%
Prolonged PTCA- >70'	15%	8.3%	3.8%	13%
40-70'	9.7%	3.6%	3.8%	8.4%
<40'	6.4%	2.9%	2%	7.7%
1 segment treated	12.3%	5.8%	3.3%	10.6%
>1 segment treated	14.8%	11.5%	3.1%	10.5%
Type C lesion	14.8%	12.1%	6.6%	12.1%
No type C lesion	12.7%	6.8%	2.7%	10.2%
Peripheral vascular disease	15.3%	16.1%	1.7%	12.9%
No peripheral vascular disease	12.9%	6.8%	3.5%	10.2%

TABLE 4.1
COMPARISON OF BLEEDING DATA AMONG THE EPIC TRIAL
AND OTHER CLINICAL TRIALS IN PATIENTS UNDERGOING ANGIOGRAPHY/PTCA

Study	n	Hemorrhagic Stroke	Patients Transfused[a]	TIMI Major Bleed	Surgery for Bleeding	Change in Hgb/Hct[b]
EPIC						
Bolus plus Infusion	708	0.3%	16.8%	10.6%	1.7%	Hgb: -2.1g/dL
rt-PA and Angiography/PTCA						
Rao *et al.*, 1988 (TIMI-I)	143	0	22.4%	15.4%	NR	NR
Topol *et al.*, 1987 (TAMI)	386	0.5%	32%	NR	NR	Hct: -11.7%
Bovill *et al.*, 1991 (TIMI-IIA)	1424	0.6%	NR	7.0%	NR	NR
Simoons *et al.*, 1988	183	0.6%	10%	NR	NR	Hct: -7%

NR = Not reported
[a] Includes patients who had CABG.
[b] Mean change in hemoglobin (Hgb) or median change in hematocrit (Hct) from pre-treatment to nadir value post-treatment.

TABLE 4.1 (continued)

COMPARISON OF BLEEDING DATA AMONG THE EPIC TRIAL
AND OTHER CLINICAL TRIALS IN PATIENTS UNDERGOING ANGIOGRAPHY/PTCA

Study	n	Hemorrhagic Stroke	Patients Transfused[a]	TIMI Major Bleed	Surgery for Bleeding	Change in Hgb/Hct[b]
Primary PTCA in MI						
Grines *et al.*, 1993	193	0%	12.3%	NR	2.1%	NR
Stents						
Lincoff *et al.*, 1993	63	NR	49%	NR	NR	NR
George *et al.*, 1993	494	0.2%	16.8%	NR	NR	NR
Hearn *et al.*, 1993	103	1%	NR	NR	6.7%	Hct: -12%

NR = Not reported
[a] Includes patients who had CABG.
[b] Mean change in hemoglobin (Hgb) or median change in hematocrit (Hct) from pre-treatment to nadir value post-treatment.

TABLE 8.3.3
CUMULATIVE NUMBERS AND PERCENTAGES OF TREATED PATIENTS WITH SAFETY/EFFICACY OUTCOMES BY SEVERITY OF OUTCOME

	Total	Placebo	Bolus	Bolus + Infusion	Predicted net benefit[a] per 1000 treated patients
Patients treated	2038	681	679	678	
Events					
Death	30 (1.5%)	12 (1.8%)	9 (1.3%)	9 (1.3%)	5
Stroke	38 (1.9%)	15 (2.2%)	12 (1.8%)	11 (1.6%)	6
Large MI[b] or urgent CABG	140 (6.9%)	61 (9.0%)	42 (6.2%)	37 (5.5%)	35
Other MI	178 (8.7%)	75 (11.0%)	58 (8.5%)	45 (6.6%)	44
Other primary endpoint[c]	225 (11.0%)	92 (13.5%)	79 (11.6%)	54 (8.0%)	55
Surgery for bleeding	244 (12.0%)	95 (14.0%)	88 (13.0%)	61 (9.0%)	50
Major bleeding[d] and serious or life-threatening hypotension	265 (13.0%)	99 (14.5%)	94 (13.8%)	72 (10.6%)	39
Severe thrombocytopenia with major bleeding[d]	266 (13.1%)	99 (14.5%)	94 (13.8%)	73 (10.8%)	37
Transfusion of >5 units of RBCs/whole blood[d]	269 (13.2%)	99 (14.5%)	94 (13.8%)	76 (11.2%)	33

[a] Placebo event rate minus bolus plus infusion event rate times 10.
[b] Q-wave or non-Q-wave with CK ≥5 times the upper limit of normal.
[c] Urgent PTCA, endpoint stent placement and endpoint IABP placement.
[d] Excludes patients who had CABG during the index hospitalization.

The bottom row in Table 8.3.3 suggests that, after accounting for any primary endpoint or the most severe safety outcomes, 33 fewer patients per 1000 would be expected to experience any of these adverse outcomes if treated with the bolus plus infusion treatment regimen rather than placebo. If the less-severe safety outcomes at the bottom of the table are considered less important in the calculation of risk and benefit, the expected treatment benefit is increased.

thrombocytopenia or hypotension, or transfusion of more than 5 units of RBCs or whole blood does little to reduce the number of patients achieving a benefit (74 per 1000 treated).

TABLE 4.3
RISK BENEFIT HIERARCHY FOR 6-MONTH FOLLOW-UP OF TREATED PATIENTS

	Total	Placebo	Bolus	Bolus + Infusion	Predicted cumulative benefit[a] per 1000 treated patients
Patients treated	2038	681	679	678	
Events					
Death	60 (2.9%)	23 (3.4%)	18 (2.7%)	19 (2.8%)	6
Stroke	66 (3.2%)	25 (3.7%)	20 (2.9%)	21 (3.1%)	6
Large MI[b] or urgent CABG	198 (9.7%)	78 (11.5%)	65 (9.6%)	55 (8.1%)	34
Other MI	250 (12.3%)	97 (14.2%)	85 (12.5%)	68 (10.0%)	42
Other primary endpoint[c]	316 (15.5%)	122 (17.9%)	114 (16.8%)	80 (11.8%)	61
Other CABG	412 (20.2%)	159 (23.3%)	145 (21.4%)	108 (15.9%)	74
Surgery for bleeding	428 (21.0%)	162 (23.8%)	154 (22.7%)	112 (16.5%)	73
Other PTCA	651 (31.9%)	241 (35.4%)	229 (33.7%)	181 (26.7%)	87
Major bleeding and serious or life-threatening hypotension	670 (32.9%)	245 (36.0%)	234 (34.5%)	191 (28.2%)	78
Severe thrombocytopenia with major bleeding	671 (32.9%)	245 (36.0%)	234 (34.5%)	192 (28.3%)	77
Transfusion of >5 units of RBCs/whole blood	673 (33.0%)	245 (36.0%)	234 (34.5%)	194 (28.6%)	74

[a] Placebo event rate minus bolus plus infusion event rate times 10.
[b] Q-wave or non Q-wave MI with CK ≥ 5 times the upper limit of normal.
[c] Urgent PTCA, endpoint stent placement and endpoint IABP placement.

Appendix 4: Briefing package for Advisory Committee

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE FEB 8 1994

FROM Chief, Bioresearch Monitoring Section, HFM-640
Center for Biologics Evaluation and Research

CONTACT Marci Schentzel HFM-640
Telephone: 301- 594-1077

CP: 7348.811 CP: 7348.809
PAC: 41811A PAC: 41809
Priority: HIGH
Due Date: 30 days

TO Director, Investigations Branch
Dallas District Office, HFR-SW150
Cincinnati District Office, HFR-MA450
Kansas District Office, HFR-SW350

PLEASE NOTE: This PLA will be reviewed by an advisory committee meeting scheduled for Thursday, June 9, 1994. This PLA is to be reviewed in a PRIORITY (six months) status under the User Fee system. We request at least the 483 from the clinical investigator portion of this assignment by April 15, 1994.

General Instructions

We request that inspections of the following clinical investigators be performed in accordance with CP 7348.811:

INVESTIGATOR

(DAL-DO)
Frank Navetta, M.D.
Mother Frances Hospital
800 E. Dawson
Tyler, TX 75701

(CIN-DO)
Stephen Ellis, M.D.
Cleveland Clinic Foundation
Dept. Of Cardiology Desk F-25
9500 Euclid Ave.
Cleveland, OH 44195-5066

(KAN-DO)
Mark Tannenbaum, M.D.
Mercy Hospital Medical Center
6th & University
Des Moines, IA 50314

We request that an inspection of the following Institutional Review Board performed in accordance with CP 7348.809. Please review the general operations during the past 2 years, and track the review of the protocol mentioned below in your inspection.

IRB [redacted] (no record of previous inspection)

PROTOCOL Protocol No. C0116T09
"A Phase III Double-Blind, Placebo-Controlled Multicenter Study of Chimeric 7E3 Fab in Patients Undergoing High Risk Coronary Angioplasty"

SPONSOR Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

IND REF BIND - #3449, #2648, #3087

PLA REF 93-1057

PRODUCT Chimeric monoclonal antibody, Fab, (c7E3) to platelets (GPIIb/IIIa) receptor

Background

Percutaneous transluminal coronary angioplasty (PTCA), is an effective method of enlarging the lumen of stenosed coronary arteries. Despite advances in technology, there is still an inherent risk of acute coronary occlusion during and after angioplasty which accounts for the major cause of in-hospital morbidity and mortality. Acute coronary occlusion during or immediately after coronary angioplasty appears to be caused by the combination of deep arterial wall injury with resultant occlusive thrombus formation. The patients who are at higher risk for thrombotic occlusion include those with acute myocardial infarction, unstable angina or high risk morphologic characteristics.

The surface of human platelets is densely populated with receptors for various adhesion molecules. The most prominent among these receptors is the fibrinogen receptor, glycoprotein IIb/IIIa. Centocor has developed a chimeric monoclonal antibody, 7E3 Fab, that selectively binds to this receptor, blocking fibrinogen binding, thus interfering with fibrinogen-mediated platelet aggregation. Chimeric 7E3 Fab is a genetically reconstructed human/mouse IgG fragment. The major direct risk of c7E3 treatment is bleeding.

This study is a Phase III, multi-center, double-blind, placebo-controlled, randomized clinical trial in patients undergoing coronary balloon angioplasty or coronary angioplasty with an FDA approved atherectomy device who are at high risk for subsequent acute ischemic complications. Approximately 2,100 patients were enrolled by approximately 50 centers. The target population comprised women, who were not of childbearing potential, and men between the ages of 18 and 80 years who were high risk for thrombotic failure following the procedure.

The primary objective of the trial was to examine whether either of two c7E3 Fab treatment regimens reduced the incidence of clinically significant ischemic complications including death, myocardial infarction and the need for urgent re-intervention following high risk coronary angioplasty. A second objective was to obtain safety data on c7E3 in high risk PTCA patients. The primary endpoint of this study was the cumulative occurrence of death, myocardial infarction, or urgent intervention in the first 30 days following the initial procedure. Treatment efficacy was based on an intent-to-treat analysis of the primary endpoint. Safety of therapy was assessed by the incidence of changes in laboratory parameters, study agent discontinuations, clinical assessment, and the incidence of adverse experiences.

[redacted] a contract research organization, performed the randomization and drug labelling for Centocor. Randomization was balanced by entry diagnosis and was blocked by acute myocardial infarction vs. all other diagnoses within each treatment site. The interim analyses were reviewed by an independent Safety and Efficacy Monitoring Committee that made recommendations on whether to continue or stop the study based on efficacy and adverse event data. A Clinical Endpoint Committee (CEC) reviewed abstracted clinical data to determine when safety and efficacy endpoints had been achieved. The CEC was blinded to treatment group.

Special Request

We request that a clinical investigator inspection and data audit be conducted. We request that the raw data for selected subjects be reviewed. Relevant documents are attached for the selected protocol. In addition to the elements in the Compliance Program, the following areas should be addressed:

GENERAL QUESTIONS

1. Please confirm that patients met the inclusion criteria for this study.

2. Confirm that copies of subject records, consent forms and case report forms are maintained by the principal investigator when several sub-investigators are involved in the study.

3. Please collect representative samples of signed consent forms for subjects in this study.

4. Check the drug allocation log to verify accurate records for the receipt and disposition of test drug.

SPECIFIC CONCERNS

5. Please obtain copies of the pre-PTCA cardiac catheterization reports using the subject summaries provided for those subjects requiring urgent PTCA classified as a primary endpoint.

6. Please obtain copies of CPK enzyme levels and EKG reports using the subject summaries for those subjects experiencing a myocardial infarction classified as a primary endpoint.

7. Please obtain copies of the cardiac catheterization report using the subject summaries for those subjects requiring coronary artery bypass graft surgery (CABG). These subjects are are designated in the subject summaries.

8. Please examine the subject summaries provided and compare these to the subjects' medical records for the following: concomitant medication, platelet count, bleeding event, efficacy event, discontinuation of study drug (if applicable), and any adverse safety event related to study drug. Please document any discrepancies you may find in the data.

9. Please examine the line listings provided for the specific identified subjects and compare these to the subjects' medical records for the following: blood pressure during the first 12 hours after infusion, hemoglobin/hematocrit levels, bleeding episodes, and thrombocytopenia. Please document any discrepancies you may find.

10. Please obtain representative samples from the subjects' records the activated clotting time (ACT) measurements taken during hours 0-12 of the infusion with relation to heparin dosing and document any discrepanicies you may find in comparison to the subject line listings.

If you find problems with the data, please call the contact person in HFM-640, and expand your review to include additional subjects' records. If significant deviations are revealed during the inspection that may have an impact on the accuracy and reliability of the data, we request that you contact our office immediately.

Please contact HFM-640 if you have any questions concerning this assignment.

Joseph P. Salewski

Joseph P. Salewski

Attachments:

- Study protocol
- Consent form
- IRB approval
- Signed 1572
- Investigator cv
- Site-specific study data
  - Patient summaries selected for questions #5-#8
  - Line listings for vital signs, bleeding episodes, and hematology values

cc: HFM-630
HFM-640 MDS
HFM-555 Roger Cohen PLA # 93-1057
HFM-594 Glen Jones
HFM-576 Rebecca Dachman
HFM-99 PLA # 93-1057
HFM-99 INDs # 2648, # 3087, # 3449
HFD-110 Victor Raczkowski
HFD-343
HFC-132
HFC-230
Chron
Reading

HFR-SW150 BIMO Coordinator
HFR-SW100 Director
HFR-MA450 BIMO Coordinator
HFR-MA400 Director
HFR-SW350 BIMO Coordinator
HFR-SW300 Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

MEMORANDUM

DATE: May 23, 1994

FROM: Chairman, Product License Application (PLA) Committee for c7E3 (abciximab) RC 6/11/94

SUBJECT: Issues for consideration for the June 9-10 Cardiovascular and Renal Drugs Advisory Committee meeting

THROUGH: Kathryn E. Stein, Ph.D., Director, Division of Monoclonal Antibodies (DMA)

Jay Siegel, M.D., Director, Division of Clinical Trial Design and Analysis (DCTDA)

TO: Director, Advisory Committee and Consultants Staff

Background

c7E3 (abciximab) is the Fab fragment of the chimeric monoclonal IgG antibody 7E3. The original murine antibody was derived from a mouse that had been immunized with washed human platelets. Hybridomas were screened for secretion of antibody that inhibited agglutination of platelets to fibrinogen-coated beads. It was subsequently determined that the antibody selectively binds to the glycoprotein IIb/IIIa located on the surface of human platelets. The antibody fails to bind to platelets of patients with Glanzmann thrombasthenia, which is known to be the result of defective or absent GPIIb/IIIa expression. Immunohistology studies on primate and human tissue reveal binding exclusively to platelets and megakaryocytes. Although 7E3 does bind to cultured endothelial cells, which express low levels of the related vitronectin receptor, the antibody does not bind to normal human blood vessels and does not activate cultured endothelial cells.

The chimeric antibody was [redacted]

c7E3 was developed for clinical use as an anti-platelet therapy to be used in the treatment of patients with diseases involving platelet aggregation, with particular emphasis on unstable angina, acute MI, and re-occlusion following thrombolysis and PTCA. The EPIC trial was performed in patients undergoing coronary angioplasty who were at high risk of ischemic complications. Patients received c7E3 or placebo given as a bolus (0.25 mg/kg) or bolus plus continuous infusion (10 ug/min for 12 hours) starting at the time of PTCA and were followed for death, MI, or need for revascularization. The PLA was submitted to CBER in December, 1993 and was given a priority designation for purposes of the review.

The PLA Committee has reviewed the manufacturing of c7E3 and determined that the sponsor is able to make consistently a product that is potent, stable, and free from contamination by adventitious agents. An inspection of the facility is scheduled for late June 1994.

Questions for your consideration are provided in the Appendix.

Materials from Centocor

Centocor has provided 2 volumes of material for review by the Cardiology and Renal Drugs Advisory Committee. Volume 1 contains information about the origin and manufacturing of c7E3, a summary of the pre-clinical and clinical data, and a detailed analysis of the pivotal EPIC trial. Volume 2 contains copies of key papers referred to in volume 1. The efficacy data and analyses in volume 1 are a subset of those presented in the PLA and have been judged by CBER reviewers to be accurate and consistent with the final analytic plan of January 29, 1993.

Issues for your consideration

I. Dose Selection

Definition of bolus and infusion doses of c7E3

The proposed dose for licensure is c7E3 Fab as a 0.25 mg/kg IV bolus followed by c7E3 mAb at 10 ug/min as a continuous IV infusion for 12 hours. The justification for the proposed bolus dose is that a bolus of at least 0.25 mg/kg is required in order to produce >80% receptor blockade, a level of receptor blockade that was shown in various pre-clinical models to be associated with efficacy. Doses in excess of 0.25 mg/kg did not cause further receptor blockade or further inhibition of platelet aggregation. The data from the critical experiment are shown in section 5.1.2 of the Centocor submission.

A continuous infusion was determined in pre-clinical and clinical studies to be required in order to maintain functional receptor blockade. Two doses were explored, —and 10 ug/min, administered for varying lengths of time ——— The 10 ug/min dose was effective at maintaining receptor blockade for the duration of an infusion (24 hours) whereas the —ug/min dose was not. The results of the key experiment are shown in section 5.1.4.3 of the Centocor submission.

The selection of a 12 hour infusion duration was based on clinical estimates of the period at risk for abrupt closure of the artery newly opened by PTCA.

The concepts of 80% receptor blockade and the need for a continuous infusion to achieve sustained receptor blockade, rather than repeated bolus doses, are supported by the pre-clinical data. The dose response data for the bolus appear to support the selected dose of 0.25 mg/kg to achieve >80% inhibition of platelet function to maximize efficacy. This was the dose studied in the phase 3 EPIC trial. The efficacy data from the EPIC trial validate platelet receptor blockade as a direct measure of the biologic activity of c7E3.

There are fewer data to support the 10 ug/min infusion dose. The data are based on evaluation of only two doses of c7E3 in a non-randomized study of a limited number of subjects with stable coronary artery disease. In that study and in the pivotal trial the sponsor chose not to adjust the maintenance dose by weight. Although the data indicate that the —ug/min maintenance dose is inadequate for achieving sustained platelet receptor blockade. ———

Fourth, the PLA Committee has attempted to verify that study blinding was maintained. Unblinding of the study drug by the treating physicians occurred in 82 patients (4% of the patients in the study) as follows: 22 placebo, 27 bolus, and 33 bolus plus infusion. The excess of unblinding in the active drug arms reflects the increased incidence of major bleeding in those arms. The circumstances of each instance of unblinding have been reviewed by examination of CRFs in the CD-ROM database for each of these patients. Unblinding was almost always performed because of bleeding or in anticipation of surgery (CABG). In those cases unblinded for CABG, the patients proceeded to CABG regardless of what was discovered by unblinding.

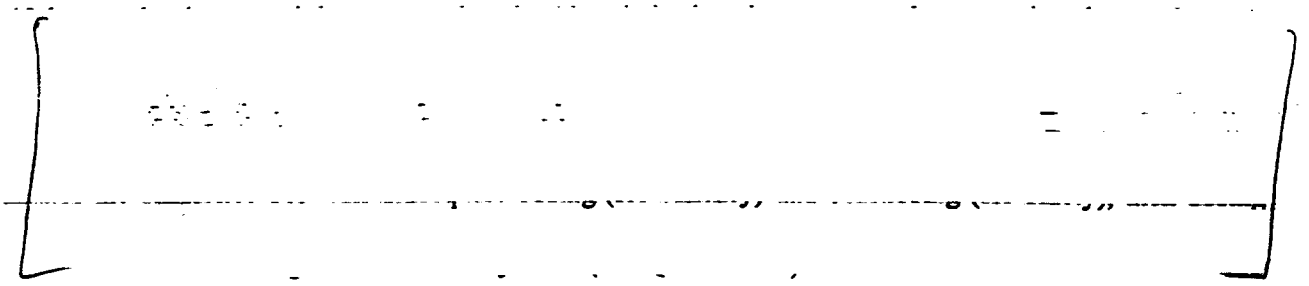
Analytic plan

The analytic plan specified intention-to-treat analyses for all 1° and 2° endpoints. Tests for treatment differences for the primary endpoint were performed in two stages at the two interim analyses and at the final analysis. The first stage in each analysis was a test for a dose-response trend across treatment groups proceeding from placebo to bolus to bolus plus infusion. For the final analysis a one-sided p-value of 0.036, adjusted for the two interim analyses, was needed to achieve statistical significance of the dose-response trend. The second stage of each analysis consisted of pairwise comparisons of each c7E3 treatment group to the placebo. One-sided p-values <0.05 were required for any comparison to demonstrate statistically significant reductions from placebo. In actuality, two-sided p-values were reported in the PLA and are used in the **Tables** below and those presented in Centocor volume 1.

The final analytic plan specified a number of 2° objectives that were prospectively ranked by order of importance as follows: analyses of components of the 1° endpoint (all-cause mortality, cardiac mortality plus non-fatal MI, MI, urgent intervention, cause-specific mortality); analysis of the 1° endpoint by patients enrolled with MI or unstable angina (acute coronary syndromes) versus other high risk groups; analyses of the 1° endpoint by the presence or absence of thrombus at the index PTCA; replication of the 1° endpoint analysis in two independent sets of data; incidence and nature of ischemic episodes; analyses of the 1° endpoint by age, gender, and study site; 6 month follow-up; and an economic analysis. The secondary analyses were intended only to be explanatory and hypothesis-generating and corrections for multiple testing were not performed.

The analytic plan underwent several revisions, all of which were reviewed and approved by CBER reviewers prior to unblinding of the database. One focus of these revisions was on the criteria for diagnosis of acute MI, one of the endpoint components for the primary efficacy analysis. The result of the revisions was to make the criteria for MI more specific for MI while sacrificing some sensitivity. This was accomplished by focussing on CPK enzyme and ECG criteria as opposed to chest pain and setting higher thresholds for CPK enzyme elevations.

A separate and independent Safety and Efficacy Monitoring Committee (SEMC), distinct from the CEC and the sponsor, was established to review and make recommendations regarding study termination or modification based on the outcome of the interim analyses. Two interim analyses were planned and performed by the TAMI Group and presented to the SEMC. The 1st interim analysis was on July 29, 1992 when 698 CRFs were included. The 2nd interim analysis was on August 26, 1992 when data from 1336 patients were available (754 patients with CRF data and the rest from summary safety data forms and unmonitored CRFs). One should note that on both occasions analysis of the primary efficacy endpoint was performed. At the 2nd interim analysis the SEMC was specifically asked not to stop the trial for a positive efficacy result prior to the enrollment of the planned 2100 patients. Based on the balance between the efficacy endpoint and safety considerations the SEMC



II. Studies of safety and efficacy

Introduction

The clinical protocol for the EPIC trial, which was designed as a multi-center, randomized, placebo-controlled, double blind study of c7E3, compared placebo to a bolus regimen and a bolus plus infusion regimen. The protocol was submitted to CBER prior to initiation of the study.

The 1° and 2° analyses of efficacy and safety presented by Centocor in volume 1 were validated by FDA reviewers and were performed in accordance with the final analytic plan.

Issues regarding the clinical data

Data integrity

Several approaches by the sponsor and CBER were intended to ensure that the database and assessment of clinical endpoints were accurate and unbiased.

First, a Clinical Endpoints Committee (CEC) was established to review all Case Report Forms (CRFs) for the occurrence of a primary endpoint and major safety events prior to unblinding. All patients were screened by computer and by the CEC coordinator. The coordinator and committee members remained blinded to treatment arm and interim results for the entire study and 6 month follow-up period. The CEC was given abstracted clinical data prepared by the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group of Durham, NC. Each patient with a suspected endpoint was reviewed by two MD committee members. If they could not agree on a classification, the full committee reviewed the data. For patients with an efficacy and safety endpoint, two different MD's reviewed each component independently. The efficacy component was always reviewed first.

Second, FDA field inspectors are presently performing site audits at seven study sites (that enrolled a total of 693 patients) as part of the bioresearch monitoring that is routinely conducted as part of CBER's pre-license inspection program. The focus of the field inspections is being guided by questions from the PLA clinical reviewers.

Third, the sponsor provided CD-ROM disks containing photographs of original CRFs on every patient in the EPIC study. CRFs for patients experiencing efficacy or safety endpoints were grouped together for ease of review. Software programs were written to facilitate CBER analysis of this large database. CBER reviewers have examined the CRFs of every patient who died, experienced intracranial hemorrhage, or had an urgent PTCA, as well as CRFs selected at random from among those patients with any efficacy endpoint or major bleed.

recommended on both occasions that the study proceed without modification.

Completeness of follow-up

Of the 2099 patients enrolled in the study, three patients were lost to follow-up at 30 days, one in each arm. At 6 months, follow-up for the components of the 1° endpoint was 99% for survival and 98.4% for acute MI and revascularization procedures.

Publication of data

The 30-day and 6-month safety and efficacy data from the EPIC trial were published in the New England Journal of Medicine (April 7, 1994) and the Lancet (April 9, 1994). It is worth noting that the protocol, data, and conclusions presented in both articles were faithful to the protocol submitted in the IND and its subsequent FDA-approved revisions, and the data in the PLA.

Analysis of the EPIC trial

Efficacy

The efficacy data are presented in Centocor volume 1 and represent a subset of the analyses submitted in the PLA.

The EPIC trial enrolled 2099 patients undergoing high-risk angioplasty at 56 centers in the US. The sponsor defined a composite primary endpoint for the EPIC trial consisting of all cause mortality, MI, or need for urgent intervention (defined as urgent PTCA, urgent CABG, or placement of an intra-coronary stent or intra-aortic balloon (IABP)). Based on an intention-to-treat analysis c7E3 was found to reduce the occurrence of the composite endpoint in a statistically significant fashion when given as a bolus plus infusion but not as a bolus dose alone, compared to placebo (**Table 1**).

Table 1: Randomized patients who experienced a primary endpoint within 30 days of trial entry

	Total (n=2099)	**Placebo** (n=696)	**Bolus** (n=695)	**Bolus + infusion** (n=708)	**Dose response p-value**
Patients with events	227 (10.8%)	89 (12.8%)	79 (11.5%)	59 (8.3%)	0.009
% reduction versus placebo			10.4%	34.8%	
p-value versus placebo			0.428	0.008	

The six month follow-up data show that the initial efficacy benefit is maintained for the entire 6 months of follow-up. The analysis of events occurring between days 30 and 180 provides evidence that the early benefits of c7E3 were not transient, i.e. did not represent postponement of complications, and suggest that some additional benefit may occur between 30 and 180 days (**Table 2**).

Table 2: Randomized patients who experienced a primary efficacy endpoint within 6 months of trial entry

	Total	Placebo	Bolus	Bolus + infusion	Dose response p-value
Patients randomized	2099	696	695	708	
Patients evaluated from Day 0	2099	696	695	708	
Number with events	322 (15.5%)	121 (17.6%)	115 (16.7%)	86 (12.3%)	0.007
% reduction versus placebo			5.2%	30.4%	
p-value versus placebo			0.651	0.006	
Patients evaluated after day 30[a]	1839	595	607	637	
Number with events	95 (5.2%)	32 (5.5%)	36 (6.0%)	27 (4.3%)	0.357
% reduction versus placebo			-8.8%	22.5%	
p-value versus placebo			0.679	0.351	

[a] Excludes patients who experienced an endpoint event (death, MI, or urgent intervention) from day 0 through 30-day follow-up.

Use of a composite endpoint for determining efficacy

One important aspect of the EPIC study was the use of a composite endpoint to determine efficacy. The use of a composite endpoint was clearly intended to increase the event rate for the primary endpoint in the trial and thus limit study size. When a composite endpoint is used, it is necessary to evaluate the relative clinical significance of each of its components (see Question #3). The clinical impact of the mortality and MI components is not in doubt. The significance of the urgent intervention component is potentially more controversial. The sponsor has attempted to address the issue of whether each component was appropriate through several prospectively defined secondary analyses of efficacy as presented below and in Centocor volume 1, Section 5.6.2.

Analysis of components of the primary endpoint

The sponsor analyzed for efficacy each component of the composite endpoint. There were few deaths (n=33, 1.6% of enrolled patients) in the trial and the number of deaths in each of the trial arms was similar. The greatest effects of c7E3 were observed in the MI/unstable angina and urgent intervention components of the composite primary endpoint and it is of note that a statistically significant reduction was observed in each of these components independently in the bolus plus infusion arm compared to placebo (**Table 3**). Within the MI component of the composite endpoint, the statistically significant

reduction in Q wave MI was the most clinically compelling (Centocor, volume 1, Figure 5.18). Efficacy can also be seen for the combined endpoint of death plus MI (**Table 3**). The component making the greatest contribution to efficacy, however, was urgent intervention (**Table 3**). Within the urgent intervention component, reduction in urgent PTCA made the greatest contribution to efficacy (Centocor volume 1, Figure 5.19). Reduction in the need for urgent CABG showed a favorable trend.

Table 3: Randomized patients with a primary endpoint by component within 30 days of trial entry

	Total (n=2099)	**Placebo** (n=696)	**Bolus** (n=695)	**Bolus + infusion** (n=708)	**Dose response p-value**
Death	33 (1.6%)	12 (1.7%)	9 (1.3%)	12 (1.7%)	0.964
% reduction versus placebo			24.8%	1.6%	
p-value versus placebo			0.511	0.963	
MI	144 (6.8%)	60(8.6%)	43 (6.2%)	37 (5.2%)	0.013
% reduction versus placebo			28.2%	39.4%	
p-value versus placebo			0.091	0.014	
Death and MI	159 (7.6%)	67 (9.6%)	49 (7.1%)	43 (6.1%)	0.012
% reduction versus placebo			26.9%	35.8%	
p-value versus placebo			0.083	0.014	
Urgent intervention	126 (6.0%)	54 (7.8%)	44 (6.4%)	28 (4.0%)	0.003
% reduction versus placebo			17.2%	49.1%	
p-value versus placebo			0.300	0.003	

There was some concern at the time the trial was designed that the urgent intervention component was a "soft" endpoint compared to death and MI in that determination of urgent need may be subject to bias more than determination of the other endpoint components. Several features of the trial design and conduct and some of the secondary analyses sought to improve the credibility of the urgent intervention endpoint. In assessing the validity of a reduction in the need for urgent PTCA, the PLA Committee took into account the following: First, the classification of PTCA as urgent was done by the CEC, which was blinded to the treatment arm throughout the trial. Second, the events leading to urgent PTCA in the trial were clearly of a serious nature, with documentation of prolonged chest pain, ECG changes, and requirement for nitroglycerin and morphine (Centocor volume 1, Table 5.16). All but two patients with an urgent PTCA endpoint had ischemic episodes reported and the two exceptions

had documented abrupt closure of the dilated coronary artery before leaving the cath lab. Third, review by the PLA Committee of the individual CRFs on CD-ROM for patients experiencing an endpoint urgent PTCA confirmed the urgent nature of the PTCAs performed in the trial. In the CRFs the urgent PTCAs were clearly distinguished from routine, non-urgent PTCA on the CRFs (most of which were staged procedures to treat multiple lesions in multiple arteries). Fourth, urgent PTCA in EPIC was not a benign procedure; many were associated with complications (Centocor volume 1, Table 5.17).

However, there are no data establishing that aside from patients who subsequently experienced MI or death and thus would have reached an endpoint anyway, patients who required urgent intervention experienced lasting morbidity or less favorable outcomes than if urgent intervention had been avoidable (see Question #3).

Appropriateness of entry criteria for the study, definition of a target population, and analysis of effects of c7E3 across subgroups

The incidence of abrupt closure of the newly opened artery following PTCA ranges from 2-25% depending on the patient population. From a variety of published studies (references in Centocor volume 2) it is clear that certain subsets of patients are at particularly high risk for complications from angioplasty. These patients include those with certain angiographic lesion patterns (types B and C, defined by the ACC/AHA task force), age >65, female gender, prior MI, diabetes, prior CABG, impaired left ventricular function, and a history of hypertension. The EPIC trial sought to focus on a high risk patient population and defined high risk angioplasty as that occurring in patients referred for elective or urgent PTCA in the setting of 1) acute coronary artery syndromes (unstable angina and/or acute or recent MI) or 2) high-risk morphologic and/or clinical characteristics (see **Table 5** below for definitions of the 10 high risk categories in the EPIC study).

It was therefore important to determine whether the benefit of c7E3 was seen in the various pre-defined strata within the trial. Primary endpoint event rates were examined first according to the broadly defined risk strata of MI and unstable angina (acute coronary syndromes) versus all other patients in the EPIC trial. **Table 4** shows that primary endpoint event rates were reduced by c7E3 across both of the broad risk strata. The benefit over the entire 6 months was also seen in both of the pre-defined 1° risk strata. Reduction at either follow-up was much more prominent, however, in the patients with acute or recent MI or unstable angina. One criticism of the study is that a minority of patients in the study (42.5%) were in this important risk stratum, which was prospectively identified as the highest risk stratum. It is worth noting further that 534 or 60% of the patients in the MI/unstable angina risk category were in stratum C5 (angioplasty of infarct-related lesion within 7 days of MI, see **Table 5**); this group of patients may be different from the group with more acute coronary syndromes. It would have been helpful to have enrolled a larger number of patients with acute coronary syndromes into the trial (see Question #4).

Table 4: Primary composite endpoint event rates within 30 days by broadly defined risk status

	Total	Placebo	Bolus	Bolus + infusion	Dose response p-value
MI or unstable angina	893	288	306	299	
Patients with events	94 (10.6%)	37 (12.8%)	36 (12.0%)	21 (7.0%)	0.025
% reduction versus placebo			6.9%	45.3%	
p-value versus placebo			0.686	0.022	
Other high risk categories	1206	408	389	409	
Patients with events	133 (11.0%)	52 (12.7%)	43 (11.1%)	38 (9.3%)	0.125
% reduction versus placebo			13.2%	27.1%	
p-value versus placebo			0.478	0.125	

The PLA Committee also felt that it was important to examine whether c7E3 bolus plus infusion treatment had beneficial effects on the occurrence of the primary endpoint in each of the 10 entry strata used in the trial. As shown in **Table 5**, there are trends in the reduction of the primary endpoint in most of the strata.

Table 5: Primary endpoint event rates by stratification criteria

	Total	Placebo	Bolus	Bolus + infusion
Unstable angina-rest (A1) Patients with events	310	104 14 (13.5%)	107 6 (5.6%)	99 4 (4%)
Unstable angina- recurrent (A2) Patients with events	143	37 6 (16.2%)	60 6 (10%)	46 3 (6.5%)
MI- early post-infarction angina (A3) Patients with events	176	57 6 (10.5%)	56 4 (7.1%)	63 3 (4.8%)
MI- direct intervention (B1) Patients with events	37	13 3 (23.1%)	11 2 (18.2%)	13 1 (7.7%)
MI- rescue angioplasty (B2) Patients with events	22	7 1 (14.3%)	8 3 (37.5%)	7 0 (0.0%)
At least 2 type B characteristics (C1) Patients with events	1662	540 67 (12.4%)	552 67 (12.1%)	570 48 (8.4%)
At least 1 type C characteristic (C2) Patients with events	357	127 18 (14.2%)	119 14 (11.8%)	111 13 (11.7%)
Female, ≥65 years, with at least 1 type B characteristic (C3) Patients with events	278	87 15 (17.2%)	92 14 (15.2%)	99 11 (11.1%)
Diabetes mellitus with at least 1 type B characteristic (C4) Patients with events	417	144 18 (12.5%)	138 9 (6.5%)	135 16 (11.9%)
MI- angioplasty of infarct-related lesion within 7 days of MI (C5) Patients with events	534	167 18 (10.8%)	184 24 (13%)	183 17 (9.3%)

N.B.: Some patients were qualified for more than one stratification criterion. The lesion characteristics (B and C) are from the ACC/AHA classification (Centocor volume 1, Table 2.1, p. 26).

Consistency of the analysis

In addition to the consistent trends favoring the c7E3 bolus plus infusion arm for the various risk strata shown in **Tables 4** and **5**, there were consistent beneficial effects regardless of patient age or gender, study site, manufacturing lot, risk group, and patients with or without visible coronary thrombus at the index PTCA. The six month follow-up data show that the initial efficacy benefit is durable.

Other clinical efficacy data

The sponsor found a trend in favor of c7E3 efficacy in a randomized, placebo-controlled phase 2 study performed in 60 patients with refractory unstable angina undergoing high risk PTCA. Patients received a c7E3 regimen similar to that used in the EPIC trial. PTCA was performed after a minimum of 18 hours of study agent exposure. Nineteen placebo patients and 11 c7E3 treated patients experienced at least 1 major clinical event, including 4 MIs (all in placebo patients). Sixteen placebo patients and 8 c7E3 patients had recurrent ischemia. A CEC performed a blinded analysis of a composite efficacy endpoint (the same endpoint as that used in EPIC) and found a lower incidence of the composite endpoint in c7E3 treated patients (3%) compared to placebo patients (23%).

Safety

Bleeding was an expected adverse event in the EPIC study given the well-characterized biological effects of c7E3 on platelets combined with the fact that the study population was on heparin and aspirin and undergoing invasive coronary procedures. The incidence of intracranial bleeds and bleeds causing patient deaths was not increased in the bolus and bolus plus infusion arms compared to placebo (Centocor volume 1, Table 5.23 and **Table 6**).

Table 6: Treated patients with strokes and deaths due to bleeding

	Placebo (n=696)	**Bolus** (n=695)	**Bolus + infusion** (n=708)
Deaths due to bleeding[a]	1 (0.1%)	0	1 (0.1%)
Hemorrhagic stroke	2 (0.3%)	1 (0.1%)	3 (0.4%)
Non-hemorrhagic stroke	2 (0.3%)	4 (0.6%)	2 (0.3%)

[a]Both bleeding-related deaths were due to hemorrhagic strokes.

The incidence of other major bleeding (major and minor criteria developed by the TIMI study group, listed in Centocor volume 1, Section 5.7, p. 126, were used) was increased 2-3 fold in the bolus plus infusion arm compared to placebo (**Table 7**).

More than 70% of the episodes of major bleeding were at the arterial access site in the groin (Centocor volume 1, Table 5.28). Most of the remaining episodes consisted of spontaneous hematemesis, hematuria, or retroperitoneal hemorrhage. It is interesting that the investigators and cardiac surgeons were apparently able to use platelet transfusions to reverse the effects of c7E3 in patients requiring CABG such that blood loss during surgery was not more severe in those who had received c7E3. Unfortunately, few data are available allowing direct analysis of this issue.

Table 7: Number of patients with bleeding events

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + infusion (n=708)	Dose response p-value
Major bleeding	222 (10.6%)	46 (6.6%)	77 (11.1%)	99 (14.0%)	<0.001
% change versus placebo			+67.6%	+111.6%	
p-value versus placebo			0.003	<0.001	
Minor bleeding	295 (14.1%)	68 (9.8%)	107 (15.4%)	120 (16.9%)	<0.001
% change versus placebo			+57.6%	+73.5%	
p-value versus placebo			0.0002	<0.001	

Bleeding in c7E3 treated patients did not lead to an increased number of surgical procedures although it did lead to a greater number of diagnostic procedures, particularly abdominal CT scans and GI endoscopies. Patients in the bolus plus infusion arm who had major bleeds more often required >5 units of PRBCs and had more episodes of serious or life-threatening hypotension than patients in the other study arms (Centocor, volume 1, Table 5.23). Bleeding was also associated with prolongation of hospital stay (median stay of 7 days in patients with a major bleed compared to a median of 3 days in patients without major bleeding).

In assessing the relative impact of the benefits and risks associated with c7E3, the following factors require consideration. One of the complications that occurred at a lower incidence in patients on c7E3 treatment compared to placebo, Q-wave MI, is irreversible and generally thought to be associated with long-term morbidity. On the other hand, other complications prevented by c7E3 such as urgent PTCA are not associated with clear long-term adverse effects. With regard to safety, the incidence of intracranial bleeding was too low in any of the groups (**Table 6**) to exclude an increase in the bolus plus infusion arm compared to placebo. c7E3 use was not associated with an observed increase compared to placebo in the incidence of fatal or intracranial hemorrhage in this study. Two of 708 (0.3%, 95% confidence intervals 0.1-1.0%) treated patients in the bolus plus infusion arm had intracranial hemorrhage (1 of these was fatal). There was a significantly increased risk of bleeding other than intracranial hemorrhage associated with c7E3 administration but it occurred predominantly at the arterial access site and this subset should therefore be amenable to local control measures and replacement therapy with blood products. Blood transfusions are not without risk, however, and bleeding did lead on occasion to life-threatening complications such as hypotension. In order to improve the assessment of risks and benefits, the PLA Committee feels that it is reasonable to analyze further any factors within the trial that may have independently contributed to or magnified the risk of bleeding. It is equally important to attempt to identify sub-groups of patients in whom the bleeding risk may be intolerably high relative to the benefits of c7E3.

Analysis of heparin effects on bleeding

In the EPIC study heparin was not given on a weight adjusted basis. A number of observations presented in Centocor volume 1 indicate that improved dosing of heparin on a per kg basis might lower the risk of bleeding. First, there was a strong statistically significant association of bleeding and body weight in c7E3 treated patients, particularly in the bolus plus infusion arm (Centocor volume 1, Figure 5.39). Similar statistically non-significant trends were seen in the bolus and placebo arms. The incidence of major bleeds was most notable in men <75 kg. A similar trend was seen in women, though not as marked.

Second, higher bolus doses of heparin were associated with higher rates of major bleeding events (Centocor, volume 1, Figure 5.41). Confirming the idea that lighter patients may have been overdosed with heparin was the parallel observation of an inverse relationship between activated clotting time (ACT) and body weight with the lowest weight group having the highest median ACT values (Centocor volume 1, Figure 5.43). Taken together, these observations suggest that adjustment of the heparin dose on a weight basis may be one appropriate means to decrease the incidence of bleeding. In contrast to the analysis of bleeding and heparin dose it is important to note that there was no relationship between heparin dose and the occurrence of the primary endpoint in any of the treatment groups (Centocor, volume 1, Figure 5.41). This latter observation provides justification for efforts to fine tune the heparin dose to decrease the incidence of bleeding and suggests that efficacy may not be compromised in the process (Question #2).

Exploratory analysis of factors influencing efficacy and major bleeding

In order to probe further the potential contributions of weight, heparin dose, and c7E3 dose to bleeding risk, the PLA Committee performed an exploratory logistic regression analysis. We first performed a univariate analysis to determine which variables had the greatest impact on outcome (**Table 8**). Important clinical and demographic variables based upon the trial entry criteria and the outcomes of pre-specified and *post hoc* subgroup analyses were analyzed in the model. Because the focus of the analysis was on bleeding risk it would have been useful to include ACT and activated partial thromboplastin time (APTT) values in the model but in both instances a large number of values was missing. This was not true for initial heparin dose which was included in the model. Weight was also examined as its reciprocal in order to evaluate the effect of heparin and c7E3 infusions expressed in terms of rates of drug delivery per kg.

The analysis in **Table 8** suggests that weight, peripheral vascular disease, duration of PTCA, PTCA success or failure, and possibly gender, had an association with the outcome of the primary endpoint. Heavier patients were more likely to benefit from treatment as were women. Patients with peripheral vascular disease, prolonged PTCAs, and failed PTCAs were less likely to benefit from treatment.

Weight was also associated with major bleeding as were age, duration of PTCA, PTCA success, and possibly entry stratum C2 and gender. Lighter patients were more likely to bleed as were older patients, women, and patients with prolonged PTCAs, failed PTCAs, or type C lesions.

Table 8: Univariate analysis of efficacy

		Primary endpoint	Major bleed
Variable	**Number of observations**	**p-values**	**p-values**
Age	2099	0.2022	0.0009
Renal disease (creatinine >2)	2099	0.94	0.6698
Entry stratum C2	2098	0.23	0.0824
Gender	2099	0.084	0.0788
Smoking history	2099	0.46	0.9422
Weight (1/weight)	2097	0.0011 (0.0015)	<0.0001 (<0.0001)
Diabetes	2096	0.43	0.5513
Peripheral vascular disease	2074	.001	0.23
Initial heparin dose	2043	0.1462	0.7825
Duration of PTCA (>70 or ≤70')	2099	<0.0001	.0001
PTCA success/failure	2099	<0.0001	<0.0001
Number of segments treated	2058	0.3427	0.5960

We next performed a multiple logistic regression analysis (**Table 9**) of efficacy using these variables. The four significant variables (weight, peripheral vascular disease, duration of PTCA, and PTCA success/failure) from the analysis in **Table 8** were used. In addition treatment with c7E3 was introduced as a variable. Interactions of treatment with PTCA success, PTCA duration, and peripheral vascular disease were explored. The only interaction that was significant was treatment by PTCA success at the p=0.058 level. This result confirms observations presented by Centocor (volume 1, Section 5.9.3, Figure 5.48). The multivariate analysis presented in **Table 9** includes the interaction of treatment by PTCA success.

Table 9: Multiple logistic regression analysis of efficacy

Variable	p-values
1/Weight	0.0002
Treatment	0.31
Peripheral vascular disease	0.0057
PTCA duration (>70' or ≤70')	<0.0001
PTCA success/failure	<0.0001
Interaction between treatment*PTCA	0.0584

In the analysis of major bleeding, four variables (age, weight, duration of PTCA, and PTCA success/failure) from the analysis presented in **Table 8** were used. In addition treatment with c7E3 was introduced as a variable. Interactions between treatment and PTCA success and duration were explored, found to be non-significant and were therefore removed from the final model. In the multivariate analysis presented in **Table 10** all factors remained significant except for age.

Table 10: Multiple logistic regression analysis of major bleeding

Variable	p-values
Age	0.207
1/Weight	<0.001
Treatment	0.0003
PTCA duration	<0.001
PTCA success/failure	<0.001

What is striking in these analyses is the persistence of the reciprocal of weight (or weight) as a significant factor associated with the occurrence of the primary endpoint and major bleeding, even when other factors are controlled for. As weight is highly correlated with the dose intensity per kg of heparin bolus and c7E3 infusion, it suggests that either of these may be an appropriate target for clinical study of alternative dosing regimens if the bleeding risk is judged to be excessively high (Question #2). A number of *post hoc* analyses have been presented by Centocor (volume 1, Section 5.9.1) suggesting that heparin dose adjustment is particularly worthy of exploration.

Additional sub-group analyses for safety and efficacy

We have attempted to identify groups of patients in the EPIC study in whom the risk to benefit ratio may be less favorable than in the rest of the study population (Question #5).

There are sub-groups of patients in EPIC who appeared to derive little or no benefit from c7E3, especially patients with adverse procedural characteristics such as an unsuccessful index PTCA (Centocor volume 1, Section 5.9.3), a prolonged index PTCA (Centocor volume 1, Section 5.9.2), a PTCA on multiple arterial segments, or at least 1 type C lesion (a tortuous or angulated lesion with diffuse involvement or a total occlusion > 3 months old, all predictive of a <60% success rate with PTCA; Centocor, volume 1, Table 2.1, p. 26 and Figures 5.35 and 5.39). The multiple logistic regression analysis performed above supports the strong interaction of PTCA success or failure with treatment outcome. It is certainly clinically plausible that if the index PTCA fails or has a very high chance of failure that the administration of c7E3 is unlikely to be of benefit. Major bleeds were more frequent in all three arms of the study in patients requiring prolonged PTCA and in patients with failed PTCA.

Patients with peripheral vascular disease appeared to be at high risk of bleeding with little benefit from c7E3 (Centocor volume 1, Figures 5.35 and 5.39). The lack of benefit may reflect the severity of the underlying disease and the bleeding risk may reflect technical difficulties in heavily diseased arteries. In this group the risk of bleeding also appeared to be greater in the bolus plus infusion compared to the other two study arms.

Patients with prior GI disease, patients receiving rescue PTCA for failed thrombolysis and those receiving thrombolytics post-PTCA or during PTCA also had a higher risk of bleeding generally, although the risks were not magnified in the bolus or bolus plus infusion arm compared to placebo. The increased risk of bleeding in these subgroups is also clinically plausible. The number of patients receiving thrombolytics in proximity to c7E3 was small, making precise assessments of efficacy and safety in these patients difficult.

Other toxicities

There was a trend towards a higher incidence of severe thrombocytopenia in the bolus plus infusion arm. Severe thrombocytopenia generally occurred within the first 24 hours. Few episodes of thrombocytopenia occurred between 7-30 days in any group. Two major bleeding episodes occurred in thrombocytopenic patients in the bolus plus infusion arm. More platelet transfusions were required in the bolus plus infusion group. The well-known association of thrombocytopenia with heparin administration makes these observations difficult to interpret. However, their predominance in the bolus plus infusion arm suggests an etiologic connection to c7E3.

Immunogenicity

Allergic responses were very rare in all three groups. Furthermore, the strategy of using a chimeric Fab fragment in order to reduce immunogenicity appears to have succeeded as only 5-6% of patients in the EPIC trial developed low titer human anti-chimeric antibodies. There are no direct data concerning the safety of re-administration of c7E3.

Roger B. Cohen, M.D.
Acting Deputy Director, DMA

Appendix

Questions for the June 9-10 Cardiovascular and Renal Drugs Advisory Committee meeting regarding Centocor c7E3 (abciximab)

Question 1

Do the clinical data currently available indicate that the product is safe and effective for the treatment of patients undergoing PTCA who are at high risk of ischemic complications?

Question 2

A single weight-adjusted bolus dose of c7E3 was selected for testing in the EPIC study. The efficacy shown in the EPIC study appears to validate the concept, based on pre-clinical studies, that achievement of >80% inhibition of platelet aggregation with the bolus dose is an appropriate pharmacodynamic target. A single infusion dose was also selected for testing in EPIC but unlike the bolus dose it was not weight adjusted. Heparin doses in the study were also not weight adjusted. In the EPIC study bleeding was more common in lighter patients. Analyses were presented suggesting that the lack of adjustment of heparin dose on a per kg basis in the EPIC trial may have contributed to a higher risk of major bleeds, particularly in lighter patients. In view of the bleeding complications seen in the EPIC trial, what additional studies should be done to optimize the bolus, infusion, and heparin regimens?

Question 3

The sponsor chose a composite endpoint of efficacy for the EPIC trial consisting of all cause mortality, MI, or need for urgent intervention (defined as need for urgent PTCA, urgent CABG, placement of an intra-coronary stent, or need for IABP). Efficacy was demonstrated for the composite endpoint and two of its three components (MI and urgent intervention). Was the use of this composite endpoint appropriate for this clinical trial? Has the sponsor convincingly shown the validity of the urgent intervention component of the composite end point as it was used in the EPIC trial? Would an effect on the need for urgent intervention alone have constituted substantial evidence of efficacy?

Question 4

The investigators enrolled a heterogeneous patient population with regard to risk factors for PTCA complications. Does the term "high risk PTCA" adequately describe the appropriate target population for c7E3? Should the sponsor be asked to acquire separate data for each of the populations at high risk? If c7E3 is approved, should the labeled indication include all the high risk categories included in the EPIC trial or should it be more narrowly, broadly or loosely defined?

Question 5

Secondary analyses by the sponsor and CBER identify certain patient populations within the trial in which the benefits of c7E3 appeared to be small or the risk of bleeding was high or a combination of these. If c7E3 is approved, do the analyses presented support specific mention or exclusion of some or all of these populations in the labeling? How should these populations be discussed to in the labelling?

Appendix 5: Advisory Committee presentation

ec 6/14/94

Good afternoon Mr. Chairman, members of the Advisory Committee, ladies and gentlemen. The next subject for discussion is c7E3, a chimeric monoclonal antibody that is proposed for use as an adjunctive therapy in patients undergoing coronary angioplasty who are at high risk of ischemic complications.

Representatives of Centocor will present the development and manufacture of their product followed by the results of their phase 3 pivotal trial and other supportive clinical data. An FDA presentation in three parts will follow. First, I will briefly discuss the review of manufacturing and pre-clinical studies, and early clinical studies leading to selection of the doses tested in the phase 3 study. Dr. Victor Raczkowski, one of three medical reviewers, will then present the PLA Committee perspective on the efficacy data. Following that I will present the agency view of the safety data. Discussion will follow thereafter.

At this point I would like to introduce Mr. Martin Page of Centocor Corporation.

Centocor presentation

Cohen's presentation- Introduction and Background

PLA Committee members slide

Before proceeding I would like to describe the contributions made by the members of the PLA Committee.

Manufacturing review slide

The PLA Committee has reviewed the manufacturing of c7E3 and determined that the

sponsor is able to make consistently a product that is potent, stable, and free from contamination by adventitious agents. Potency is measured by _____

CBER has scheduled an inspection of the facility for later this month at which time Centocor will manufacture the _____ lots.

Pre-clinical studies slide

As you have heard, the c7E3 monoclonal antibody is highly specific for the human platelet and inhibits platelet aggregation by binding to the GPIIb/IIIa receptor and does so without activating platelets or blocking platelet adhesion. Receptor blockade and inhibition of platelet aggregation are highly correlated with 80% occupancy of receptors leading to nearly complete inhibition of platelet aggregation. Study of the antibody effects in several well-defined animal models of thrombosis validated the concept that doses of antibody leading to more than 80% receptor blockade would prevent arterial thrombosis.

Dose selection slide

You have heard from the sponsor the rationale, based on phase 1 data, for the size of the bolus and infusion doses as well as the clinical rationale for the infusion duration. The concepts of a loading dose to achieve immediate 80% receptor blockade and the need for a continuous infusion to maintain receptor blockade are supported by the data that were presented earlier. The efficacy data from the EPIC trial validate platelet receptor blockade as a measure of the biologic and clinical activity of c7E3. The size of the bolus dose is adequately supported by the phase 1 dose ranging studies. The phase 1 and 2 data presented in support of the infusion dose are less comprehensive. It is clear from the phase 1 data that a _____ maintenance dose does not lead to

sustained receptor blockade and inhibition of platelet aggregation. You will recall that the animal models had demonstrated that sustained receptor blockade is required for prevention of thrombosis in the animal models. Sustained receptor blockade is achieved by the 10 ug/min dose, which was the maintenance dose tested in the pivotal trial. Thus, the sponsor has narrowed the correct maintenance dose of c7E3 to within a two-fold range of between ———————. The initial heparin bolus doses and supplemental doses were based on the individual institutions' standard of care.

Data integrity slide

Before turning to Dr. Raczkowski I would like to point out several features of the EPIC trial and of our review that were designed to ensure the integrity of the data. First, the determinations of efficacy and safety endpoints were made by a CEC that was blinded to treatment arms for the entire trial and 6 month follow-up. Second, the interim analyses were conducted by a SEMC that was independent from Centocor. Third, we have performed field audits as part of our routine bioresearch monitoring program of seven of the 56 study sites accounting for more than 1/3 of enrolled patients. The auditors have reported no problems that would affect the interpretation of the clinical trial data. Finally, Centocor provided photographs of CRFs on CD-ROM disks for all 2099 patients in the EPIC trial. The PLA Committee has used this computerized database to verify the accuracy of the data presented in the PLA.

Dr. Raczkowski will now discuss the efficacy data.

Dr. Raczkowski's presentation- Efficacy

Cohen's presentation- Safety

Aside from bleeding, toxicity from c7E3 was minimal. Bleeding was an expected adverse event in the EPIC study. The questions for consideration this afternoon are first, how serious the bleeding complications were; second, whether the risks of bleeding are acceptable given the drug's benefits; and third, whether the EPIC trial data reveal any straightforward measures that might be taken to maximize the benefit to risk ratio.

You have seen, as shown in the next slide, that the incidence of major and minor bleeding was increased unequivocally 2-3 fold in the bolus plus infusion arm compared to placebo. Major bleeding was also increased in the bolus arm compared to placebo. Indeed, the biggest increase in bleeding occurs when the bolus dose is added to the aspirin and heparin regimen. Minor bleeding was also increased in both treatment arms. I shall not discuss minor bleeds further.

Number of patients with bleeding events

	Total (n=2099)	**Placebo** (n=696)	**Bolus** (n=695)	**Bolus + infusion** (n=708)	**Dose response p-value**
Major bleeding	222 (10.6%)	46 (6.6%)	77 (11.1%)	99 (14.0%)	<0.001
% change versus placebo			+67.6%	+111.6%	
p-value versus placebo			0.003	<0.001	

Minor bleeding	295 (14.1%)	68 (9.8%)	107 (15.4%)	120 (16.9%)	<0.001
% change versus placebo			+57.6%	+73.5%	
p-value versus placebo			0.0002	<0.001	

To put the bleeding risk from c7E3 in perspective, the PLA Committee considered the following:

First, the frequency of major bleeding was quite similar to, and certainly not higher, than that seen in other published clinical trials of patients undergoing angioplasty. It is noteworthy that the database accumulated as a result of the EPIC trial now provides the most accurate assessment of what the bleeding risk in high risk angioplasty actually is.

Second, the episodes of major bleeding do not appear, in general, to have been associated with serious medical complications. The most serious type of bleeding that could have occurred would have been that leading to or associated with death or irreversible morbidity. The **next slide** shows data that you have already seen in order to reiterate the point that the incidence of death due to bleeding and incidence of hemorrhagic stroke were <u>not</u> increased by c7E3 in either the bolus or bolus plus infusion arms compared to placebo.

Randomized patients with strokes and/or deaths due to bleeding

	Placebo (n=696)	Bolus (n=695)	Bolus + infusion (n=708)
Deaths due to bleeding[a]	1 (0.1%)	0	1 (0.1%)
Hemorrhagic stroke	2 (0.3%)	1 (0.1%)	3 (0.4%)
Non-hemorrhagic stroke	2 (0.3%)	4 (0.6%)	2 (0.3%)

[a]Both bleeding-related deaths were due to hemorrhagic strokes.

These data are reassuring. It is worth noting, though, that the incidence of intracranial bleeding was too low in any of the groups to exclude completely an increase of such bleeding in either c7E3 arm compared to placebo. The data shown in the slide are for all randomized patients. One of the 3 patients with hemorrhagic stroke never received c7E3. Thus, two of 678 treated patients, or 0.3%, of patients in the bolus plus infusion arm experienced intracranial hemorrhage (1 of which was fatal). The 95% confidence intervals around the 0.3% point estimate are 0.03-1.1%. The true incidence therefore probably does not exceed 1.1% but cannot be known with certainty at this time.

More than 70% of the episodes of major bleeding were at the arterial access site in the groin. The remaining episodes were a mixture of spontaneous hematemesis, hematuria, or retroperitoneal hemorrhage. Importantly, bleeding in the treatment arm did not lead to an increased number of surgical procedures and it is of great interest that bleeding associated with CABG was not more severe in patients receiving c7E3. One can infer from this that surgeons were able to manage successfully patients who had received c7E3, presumably via transfusions of platelets to reverse the drug effects.

Major bleeding did lead to a greater number of diagnostic procedures, particularly abdominal scans and GI endoscopies. Patients with major bleeds more often required transfusion with >5 units of red cells and experienced more episodes of serious or life-threatening hypotension. Bleeding was also associated with prolongation of hospital

stay.

In assessing the overall benefits and risks from c7E3, the following considerations need to be balanced. On the benefit side, a critical complication of PTCA, Q-wave MI, whose frequency was diminished by c7E3 treatment, is irreversible and generally thought to be associated with long-term morbidity. On the other hand, some of the other complications prevented by c7E3 such as urgent PTCA, are not associated with clear long-term adverse effects. On the risk side, there is no question that the addition of c7E3 to aspirin and heparin caused a significantly increased risk of bleeding but it did not cause an increased frequency of irreversible side effects such as death and stroke. Most bleeding was at the arterial access site and at least in that particular subset should be readily amenable to local control measures and replacement therapy with blood products.

In order to improve the assessment of risks and benefits for this product, the PLA Committee felt that further *post hoc* analyses of safety and efficacy were appropriate to identify factors that may have independently contributed to or magnified the risk of bleeding. We also wished to identify, whenever possible, sub-groups of patients in whom the bleeding risk may be high relative to the benefits of c7E3.

We first performed a univariate analysis to identify variables with the greatest impact on the occurrence of safety and efficacy endpoints. We tested a large number of clinical and demographic variables that were based upon the trial entry criteria and the outcomes of the many pre-specified and *post hoc* subgroup analyses performed by the sponsor, which you have already seen. These included age, renal function, type C lesion characteristics, gender, smoking history, diabetes, peripheral vascular disease, initial heparin dose, PTCA duration, PTCA outcome, number of coronary artery segments treated by PTCA, weight and the reciprocal of weight. Note that we

examined weight in two ways, as weight alone and as its reciprocal. Evaluation of weight as its reciprocal was intended to help us examine the effects in the model of the c7E3 maintenance infusion dose. The maintenance dose was set at a constant dose of 10 ug/minutes for all patients in the bolus plus infusion arm. One divided by weight is therefore proportional to the rate of drug delivery per kg.

The univariate analysis suggested that weight, peripheral vascular disease, duration of PTCA, PTCA outcome, and possibly gender, had an association with the occurrence of the primary endpoint. With regard to the safety outcome of major bleeding weight also appeared as an important variable associated with the occurrence of a major bleed. Age, duration of PTCA, PTCA success, and possibly entry stratum C2 and gender, also emerged as significant variables for the occurrence of a major bleed.

Univariate analysis of efficacy

		Primary endpoint	**Major bleed**
Variable	**Number of observations**	**p-values**	**p-values**
Age	2099	0.2022	0.0009
Renal disease (creatinine >2)	2099	0.94	0.6698
Entry stratum C2	2098	0.23	0.0824
Gender	2099	0.084	0.0788
Smoking history	2099	0.46	0.9422
Weight (1/weight)	2097	0.0011 (0.0015)	<0.0001 (<0.0001)
Diabetes	2096	0.43	0.5513
Peripheral vascular disease	2074	.001	0.23
Initial heparin dose	2043	0.1462	0.7825
Duration of PTCA (>70 or ≤70')	2099	<0.0001	.0001
PTCA success/failure	2099	<0.0001	<0.0001

Number of segments treated	2058	0.3427	0.5960

We next performed a multiple logistic regression analysis of efficacy using four co-variates that were determined to be associated with the primary endpoint: weight, peripheral vascular disease, duration of PTCA, and PTCA outcome. This analysis is shown in the next slide. In addition, treatment with c7E3 was now introduced as a variable. Interactions of treatment with each of the co-variates were individually explored. The only interaction that suggested significance was treatment by PTCA outcomes at the p=0.058 level. The slide illustrates the interaction with PTCA outcome so that treatment is no onger significant. In the absence of this interaction treatment is highly significant. This result suggests that Centocor's observations that the effects of c7E3 differed in patients according to PTCA outcome may be correct. The co-efficients in the slide are the slopes of the logit regression and reveal the direction of the associations. The associations with occurrence of an efficacy endpoint are as follows. Heavier patients were less likely to experience an endpoint. Patients with peripheral vascular disease, prolonged PTCAs, and failed PTCAs were more likely to experience an endpoint.

Multiple logistic regression analysis of efficacy

Variable	p-values
1/Weight	0.0002
Treatment	0.31
Peripheral vascular disease	0.0057
PTCA duration (>70' or ≤70')	<0.0001
PTCA success/failure	<0.0001
Interaction between treatment*PTCA	0.0584

In the multiple logistic regression analysis of major bleeding, shown in the next slide, four variables, age, weight, duration of PTCA, and PTCA outcome that were found to

be significant in the univariate analysis were used. In addition, treatment with c7E3 was introduced. Interactions between treatment and each of the co-variates were explored. The only interaction that suggested posible significance at the p=0.17 level was weight. We chose to illustrate in the slide the outcome of the model without any of the interactions. In the multivariate analysis presented in the slide all factors remained significant except for age. The associations are as follows. Lighter patients were more likely to experience a safety endpoint as were patients with prolonged PTCAs and failed PTCAs. Note that the association with weight is in different directions for safety and efficacy.

Table 10: Multiple logistic regression analysis of major bleeding

Variable	p-values
Age	0.207
1/Weight	<0.001
Treatment	0.0003
PTCA duration	<0.001
PTCA success/failure	<0.001

These multivariate analyses reveal several things. I will first discuss the co-variate of weight. It is striking that weight (or its reciprocal) emerges as a significant factor in the occurrence of the primary endpoint and safety endpoints, even when other factors are controlled for.

It is therefore worth noting again that the influence of weight on efficacy and safety is in opposite directions. Heavier patients experience more efficacy than lighter patients but less bleeding risk. The converse appears to be the case for the lighter patients. The reasons for this are not immediately obvious although a variety of post-hoc explanations are possible and have been presented already.

We would simply point out that weight is correlated with the dose intensity per kg of both the heparin bolus and the c7E3 infusion, and we would remind you that neither the heparin regimen nor the infusion dose of c7E3 were adjusted for body weight. Thus, those patients who received the largest heparin boluses and greatest dose intensity per kg of c7E3 infusion were less likely to benefit and more likely to bleed. Consequently, exploration of variations in the c7E3 infusion dose and heparin regimen may be appropriate areas for investigations aimed at enhancing the benefit to risk ratio. We agree with the sponsor that of the two drugs, heparin is probably the more promising first choice.

The multivariate analyses also point to certain subpopulations of patients within the trial in whom the risk to benefit ratio may be less favorable than in the rest of the study population. These are listed in the next slide along with others from the PLA. Most of them are medically intuitive. We wish to emphasize that all of these analyses need to be interpreted cautiously given their post hoc nature and in some instances the small number of patients.

Among the patients with an inferior benefit-to-risk ratio are those with adverse procedural characteristics such as an unsuccessful (or unattempted) PTCA, a prolonged PTCA, a PTCA or multiple arterial segments, and type C lesions. These patients experience diminshed benefit from c7E3. Patients requiring prolonged PTCA and those with failed PTCA are also appear at higher risk of bleeding complications in all three study arms.

Patients with peripheral vascular disease not only experienced little benefit but also appeared to be at higher risk of bleeding in the bolus plus infusion arm compared to the placebo arm.

Lastly, patients with prior GI disease, patients receiving rescue PTCA for failed thrombolysis and those receiving concomitant thrombolytics also had a higher risk of bleeding in all treatment arms. The increased risk of bleeding in patients with prior GI disease may be preventable with medical management. The interaction of c7E3 with thrombolytics is clearly of great interest but the number of patients receiving thrombolytics in proximity to c7E3 was small, making formal assessments of safety or efficacy in this subgroup difficult.

In summary, the Committee has found that c7E3 is potent and has clinically important effects on the occurrence of complications related to PTCA, particularly acute Q wave MI. Patients with unstable angina appear to benefit particularly from c7E3. The reduced incidence of acute MIs and urgent PTCAs in patients receiving the bolus plus infusion regimen appears to validate the concept developed in the pre-clinical studies that in vitro measures such as GPIIb/IIIa receptor occupancy and inhibition of platelet aggregation were an appropriate basis for dose selection. Despite nearly complete inhibition of platelet aggregation, c7E3 administration was not associated with an increased incidence of intracranial hemorrhage in this study. There was, however, an unambiguous increase in the incidence of major bleeding associated with c7E3. We are asking the Advisory Committee for guidance in further assessment of the benefit to risk ratio for this biologic and for advice regarding any measures that the sponsor might explore in the future to reduce the bleeding risk. Thank you very much for your attention.

1

Product License Application (PLA) Committee for c7E3 (abciximab)

Anti-GPIIb/IIIa monoclonal antibody

2

PLA Committee Members

- Roger B. Cohen, M.D.- Chair
- Glen Jones, Ph.D.- Regulatory Coordinator
- Julia Goldstein, M.D.- Product Reviewer
- Lyn Olson, Ph.D.- GMPs and Product
- Rebecca Dachman, M.D.- Clinical
- Victor Raczkowski, M.D.- Clinical
- Doug Roberts, M.D.- Clinical Pharmacology
- Barbara Davit-Myers, Ph.D.- Preclinical Pharmacology
- Ghanshyam Gupta, Ph.D.- Biostatistics

3

Manufacturing Review

- The sponsor is able to manufacture consistently a product that is pure, potent, and stable
- Potency is measured by —
- An inspection of the manufacturing facility is scheduled for late June, 1994

4

Pre-clinical Studies

- Specificity of c7E3 binding
- Correlation of GPIIb/IIIa blockade and inhibition of platelet aggregation
- Animal efficacy models
  - Definition of the extent of receptor blockade required for prevention of thrombosis

5

Dose Selection

- Selection of the bolus dose
- Selection of the infusion dose
- Selection of the infusion duration
- Selection of the heparin dose

6

Data Integrity

- Use of a Clinical Endpoints Committee (CEC)
- Use of a Safety and Efficacy Monitoring Committee (SEMC)
- Routine bioresearch monitoring by FDA
- Computer-assisted review of Case Report Forms on CD-ROM disks

7

Efficacy

8

Randomized patients who experienced a primary endpoint within 30 days of trial entry

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + infusion (n=708)	Dose response p-value
Patients with events	227 (10.8%)	89 (12.8%)	79 (11.5%)	59 (8.3%)	0.009
% reduction vs. placebo			10.4%	34.8%	
p-value vs. placebo			0.428	0.008	

9

Randomized patients who experienced a primary efficacy endpoint within 6 months of trial entry

	Total	Placebo	Bolus	Bolus + infusion	Dose response p-value
Patients randomized	2099	696	695	708	
Patients evaluated from Day 0	2099	696	695	708	
Number with events	322 (15.5%)	121 (17.6%)	115 (16.7%)	86 (12.3%)	0.007
% reduction			5.2%	30.4%	
p-value			0.651	0.006	
Patients evaluated after day 30	1839	595	607	637	
Number with events	95 (5.2%)	32 (5.5%)	36 (6.0%)	27 (4.3%)	0.357
% reduction			-8.8%	22.5%	
p-value			0.679	0.351	

10

Use of a composite endpoint for determining efficacy

- Increases the event rate for the primary endpoint in the trial
- The relative clinical significance of each component requires assessment
- Of the three components, urgent intervention requires the most scrutiny

11

Randomized patients with a primary endpoint by component within 30 days of trial entry

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + infusion (n=708)	Dose response p-value
Death	33 (1.6%)	12 (1.7%)	9 (1.3%)	12 (1.7%)	0.964
% reduction			24.8%	1.6%	
p-value			0.511	0.963	
MI	144 (6.8%)	60 (8.6%)	43 (6.2%)	37 (5.2%)	0.013
% reduction			28.2%	39.4%	
p-value			0.091	0.014	
Death and MI	159 (7.6%)	67 (9.6%)	49 (7.1%)	43 (6.1%)	0.012
% reduction			26.9%	35.8%	
p-value			0.083	0.014	
Urgent intervention	126 (6.0%)	54 (7.8%)	44 (6.4%)	28 (4.0%)	0.003
% reduction			17.2%	49.1%	
p-value			0.300	0.003	

12

Urgent intervention

- The classification of PTCA as urgent was done in a blinded fashion by the CEC
- Events leading to urgent PTCA in the trial were ischemic in nature
- The PLA Committee has reviewed individual CRFs for patients experiencing an endpoint urgent PTCA and concurs with the CEC assessments
- Urgent PTCA in EPIC was often associated with complications

13

Appropriateness of entry criteria for the study, definition of a target population, and analysis of effects of c7E3 across subgroups

14

Primary composite endpoint event rates within 30 days by broadly defined risk status

	Total	Placebo	Bolus	Bolus + infusion	Dose response p-value
MI or unstable angina	893	288	306	299	
Patients with events	94 (10.6%)	37 (12.8%)	36 (12.0%)	21 (7.0%)	0.025
% reduction			6.9%	45.3%	
p-value			0.686	0.022	
Other high risk categories	1206	408	389	409	
Patients with events	133 (11.0%)	52 (12.7%)	43 (11.1%)	38 (9.3%)	0.125
% reduction			13.2%	27.1%	
p-value			0.478	0.125	

15

Primary endpoint event rates by stratification criteria

	Total	Placebo	Bolus	Bolus + Infusion
Unstable angina - rest (A1) Patients with events	310	104 14 (13.5%)	107 6 (5.6%)	99 4 (4%)
Unstable angina - recurrent (A2) Patients with events	143	37 6 (16.2%)	60 6 (10%)	46 3 (6.5%)
MI - early post-infarction angina (A3) Patients with events	176	57 6 (10%)	56 4 (7.1%)	63 3 (4.8%)
MI - direct intervention (B1) Patients with events	37	13 3 (23.1%)	11 2 (18.2%)	13 1 (7.7%)
MI - rescue angioplasty (B2) Patients with events	22	7 1 (14.3%)	8 3 (37.5%)	7 0 (0.0%)

16

Primary endpoint event rates by stratification criteria, cont'd.

	Total	Placebo	Bolus	Bolus + Infusion
At least 2 type B characteristics (C1) Patients with events	1662	540 67 (12.4%)	552 67 (12.1%)	570 48 (8.4%)
At least 1 type C characteristic (C2) Patients with events	357	127 18 (14.2%)	119 14 (11.8%)	111 13 (11.7%)
Female, >=65 years, with at least 1 type B characteristic (C3) Patients with events	278	87 15 (17.2%)	92 14 (15.2)	99 11 (11.1%)
Diabetes with at least 1 type B characteristic (C4) Patients with events	417	144 18 (12.5%)	138 9 (6.5%)	135 16 (11.9%)
MI-angioplasty of infarct-related lesion within 7 days (C5) Patients with events	534	167 18 (10.8%)	184 24 (13%)	183 17 (9.3%)

18

Safety

19

Treated patients with strokes and deaths due to bleeding

	Placebo (n=696)	Bolus (n=695)	Bolus + infusion (n=708)
Deaths due to bleeding	1 (0.1%)	0	1 (0.1%)
Hemorrhagic stroke	2 (0.3%)	1 (0.1%)	3 (0.4%)
Non-hemorrhagic stroke	2 (0.3%)	4 (0.6%)	2 (0.3%)

Number of patients with bleeding events

	Total (n=2099)	Placebo (n=696)	Bolus (n=695)	Bolus + infusion (n=708)	Dose response p-value
Major bleeding	222 (10.6%)	46 (6.6%)	77 (11.1%)	99 (14.0%)	<0.001
% change vs. placebo			+67.6%	+111.6%	
p-value vs. placebo			0.003	<0.001	
Minor bleeding	295 (14.1%)	68 (9.8%)	107 (15.4%)	120 (16.9%)	<0.001
% change vs. placebo			+57.6%	+73.5%	
p-value vs. placebo			0.0002	<0.001	

Consistency of the analysis

- Age
- Gender
- Study site
- Manufacturing lot
- Geographic region (East, South, Middle, West)
- Hospital size (>70 vs. <70 enrollees)
- Hospital type (academic vs. non-academic)

Univariate analysis of efficacy

		Primary endpoint	Major bleed
Variable	Number of observations	p-value	p-value
Age	2099	0.3822	0.0089
Renal disease (creatinine >2)	2099	0.94	0.6698
Entry stratum C2	2098	0.23	0.0824
Gender	2099	0.884	0.9788
Smoking history	2099	0.46	0.9422
Weight (1/weight)	2097	0.0011 (0.0015)	<0.0001 (<0.0001)
Diabetes	2096	0.43	0.5513
Peripheral vascular disease	2074	.001	0.23
Initial heparin dose	2043	0.1462	0.7825
Duration of PTCA (>70'or <=70')	2099	<0.0001	.0001
PTCA success/failure	2099	<0.0001	<0.0001
Number of segments treated	2058	0.3427	0.5960

Multiple logistic regression analysis of efficacy

Variable	Parameter estimate +/- SE	p-value
1/Weight	- 109 +/- 29.7	0.0002
Bolus + infusion vs. placebo	0.19 +/- 0.14	0.18*
Bolus vs. placebo	- 0.002 +/- 0.13	0.98*
Peripheral vascular disease	0.32 +/- 0.12	0.0057
PTCA duration (>70' or <=70')	0.38 +/- 0.08	<0.0001
PTCA success/failure	-1.06 +/- 0.10	<0.0001
Interaction between treatment*PTCA	-	<0.0584

* Not meaningful in the presence of interaction

Multiple logistic regression analysis of major bleeding

Variable	Parameter estimate +/- SE	p-value
Age	- 0.010 +/- 0.0078	0.207
1/Weight	146.6 +/- 30.30	<0.001
Bolus + infusion vs. placebo	0.40 +/- 0.11	<0.0001
Bolus vs. placebo	0.06 +/- 0.11	0.61
PTCA duration	- 0.34 +/- 0.08	<0.001
PTCA success/failure	0.98 +/- 0.10	<0.001

Additional sub-group analyses for safety and efficacy

- Adverse procedural characteristics
  - Unsuccessful index PTCA
  - Prolonged index PTCA
  - PTCA on multiple arterial segments
  - At least 1 Type C lesion
- Underlying cardiovascular disease
  - Peripheral vascular disease
- Concomitant medical illness
  - Prior GI disease
- Concomitant medications
  - Patients receiving rescue PTCA for failed thrombolysis
  - Thrombolytics post-PTCA or during PTCA

Question 1

27

Do the clinical data currently available indicate that the product is safe and effective for the treatment of patients undergoing PTCA who are at high risk of ischemic complications?

Question 2

26

A single weight-adjusted bolus dose of c7E3 was selected for testing in the EPIC study. Theefficacy shown in the EPIC study appears to validate the concept, based on pre-clinical studies, that achievement of >80% inhibition of platelet aggregation with the bolus dose is an appropriate pharmacodynamic target. A single infusion dose was also selected for testing in EPIC but unlike the bolus dose it was not weight adjusted. Heparindoses in the study were also not weight adjusted. In the EPIC study bleeding was more common in lighter patients. Analyses were presented suggesting that the lack of adjustment of heparin dose on a per kg basis in the EPIC trial may have contributed to a higher risk of major bleeds, particularly in lighter patients. In view of the bleeding complications seen in the EPIC trial, what additional studies should be done to optimize the bolus, infusion, and heparin regimens?

Question 3

24

The sponsor chose a composite endpoint of efficacy for the EPIC trial consisting of all cause mortality, MI, or need for urgent intervention (defined as need for urgent PTCA, urgent CABG, placement of an intra-coronary stent, or need for IABP). Efficacy was demonstrated for the composite endpoint and two of its three components (MI and urgent intervention). Was the use of this composite endpoint appropriate for this clinical trial? Has the sponsor convincingly shown the validity of the urgent intervention component of the composite endpoint as it was used in the EPIC trial? Would an effect on the need for urgent intervention alone have constituted substantial evidence of efficacy?

Question 4

28

The investigators enrolled a heterogeneous patient population with regard to risk factors for PTCA complications. Does the term "high risk PTCA" adequately describe the appropriate target population for c7E3? Should the sponsor be asked to acquire separate data for each of the populations at high risk? If c7E3 is approved, should the labeled indication include all the high risk categories included in the EPIC trial or should it be more narrowly, broadly or loosely defined?

Question 5

25

Secondary analyses by the sponsor and CBER identify certain patient populations within the trial in which the benefits of c7E3 appeared to be small or the risk of bleeding was high or a combination of these. If c7E3 is approved, do the analyses presented support specific mention or exclusion of some or all of these populations in the labeling? How should these populations be discussed in the labeling?